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Contents on Inside Cover

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American Heart Journal

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Editorial Comment

IN the January issue, it was announced that beginning with the March, 1955, issue, there would appear in INTERLINGUA an abstract of each article.

The Editorial Board, for several years, have given serious consideration to printing abstracts in languages other than English. They were prompted in this by the fact that over 30 per cent of the circulation of the AMERICAN HEART JOURNAL is to countries outside of North America. However, to be impartial to this group of subscribers, it would have been necessary for the abstracts to appear, in addition to English, in French, Spanish, and German. This immediately presented a problem of major proportions, and on further exploration the plan was deemed to be impracticable. Those of our readers who attended the Second World Congress of Cardiology in Washington last September will have had the opportunity of seeing this international language in practical operation. INTERLINGUA is a language based upon the utilization of many words that are common to most languages. A practitioner of medicine who can read any of the Romance or Germanic languages can read INTERLINGUA with very little practice.

The adoption by the AMERICAN HEART JOURNAL of this policy will require that the author submit with his manuscript an abstract of not more than 150 words. Suggestions for writing an abstract may be obtained from the publishers of the Journal on request.

It is the hope of the Editorial Board that the introduction of abstracts in INTERLINGUA will make the Journal of greater service to all its readers.

Editor.

Original Communications

THE CLINICAL AND ELECTROCARDIOGRAPHIC DIFFERENTIATION OF SUPRAVENTRICULAR AND VENTRICULAR TACHYCARDIAS WITH REGULAR RHYTHM

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THE diagnosis of tachycardia with regular rhythm is a frequent clinical problem, and the importance of determining the exact nature of the disorder needs no emphasis. It is customary to divide the tachycardias into supraventricular and ventricular, depending on the site of origin of the pacemaker. In the former, the impulse may arise in the sinus node, the auriculoventricular node (A-V), or the auricles giving rise to sinus tachycardia, auricular tachycardia, and auricular flutter, respectively; in the latter, the ectopic focus originates anywhere in either ventricle below the A-V node.

Ventricular tachycardia has long been regarded as a more serious disturbance of rhythm, occurring predominantly in patients with serious organic heart disease.[1-7] The added strain of the tachycardia may precipitate grave complications in a heart already embarrassed.[1,2] Prompt diagnosis and treatment are imperative in this medical emergency. Digitalis, so useful in a supraventricular tachycardia, is often contraindicated in ventricular tachycardia;[2,8,9] in fact it frequently appears to precipitate this disturbance.[5,10-12] The regular supraventricular tachycardias, on the other hand, usually have no such ominous associations.[7,15,19,20,53] Although the unitary nature of the auricular arrhythmias has been proved,[13,14,17] the differentiation of auricular flutter is of clinical importance as it is a more serious disorder and more difficult to control.[7,16,18]

Certain clinical distinguishing features of limited value have been described with particular references to rate,[5,19] absolute regularity,[5,7,20-22] response to carotid sinus compression,[1,20] respiration,[15] and exercise.[13] With the advent of electrocardiography sufficient attention is no longer paid to clinical examination. As long ago as 1920, Gallavardin drew attention to Mackenzie's observation of the slow independent auricular jugular venous pulsations in ventricular tachy-

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cardia.[23] On the other hand, in auricular flutter the rapid "a" waves may suggest the diagnosis.[13] Levine has drawn attention to certain important auscultatory features. In supraventricular tachycardia the intensity of the first heart sound is usually constant, whereas in ventricular tachycardia it often varies considerably.[1,20]

If immediate recourse to the electrocardiogram is made, the clinical signs are apt to be neglected. This is unfortunate, as they may provide information which is not furnished by the conventional electrocardiogram (ECG). Indeed, on occasion, they alone may establish the diagnosis when the ECG is inconclusive. The ECG may be decisive in supraventricular tachycardia with normal conduction, but in the presence of abnormal intraventricular conduction, unless the P waves are clearly visible,[24] differentiation between supraventricular tachycardia with bundle branch block and true ventricular tachycardia is impossible.[24,25]

It is the purpose of this paper to emphasize the importance of careful auscultation and the examination of the jugular venous pulse.[26-28] We also wish to present a new auscultatory sign which we believe to be of considerable value in the differentiation of supraventricular from ventricular tachycardia. Furthermore, the value of the esophageal electrode in recording auricular activity[13,29-33,72] is demonstrated, particularly where intraventricular conduction disturbance exists.

CLINICAL MATERIAL AND METHODS

During the past two years we have encountered seventy-nine cases of paroxysmal tachycardia with regular rhythm. However, only those cases in whom we were able to confirm the clinical findings by simultaneous sound and by jugular venous and electrocardiographic tracings form the basis of this study.

In addition to full clinical examination, special attention was paid to the jugular venous pulsations and to auscultation.

Internal jugular venous pulsations were carefully inspected while palpating the opposite common carotid artery. Though it was usually impossible to identify the individual venous waves at these rapid rates, gross dissociation between auricular and ventricular rates could usually be detected. Special effort was made to identify the presence or absence of "Cannon A" waves and when present, their regularity or irregularity was noted. During auscultation attention was concentrated on the first and second heart sounds at the mitral area (MA), the fourth left space at the sternal edge (4LS), and the pulmonary area (PA). The presence or absence of any variation in the intensity of the first heart sound during held respiration was noted. Particular care was paid to the presence or absence of splitting of the heart sounds and to the degree of splitting when present. Splitting of the first heart sound was best heard at the 4LS and of the second heart sound at the PA.

The Sanborn-Stethocardiette was used to obtain phonocardiograms in each case. Logarithmic (high frequency) sound tracings, which give an accurate graphic representation of human hearing,[34,35] were recorded synchronously with a suitable electrocardiographic lead, carotid or jugular pulse tracing. The sound recordings were taken in succession from the MA, 4LS, and PA. Tracings were

TABLE I. THE DIFFERENTIATION OF TACHYCARDIAS WITH REGULAR RHYTHM

	QRS	TYPE	TOTAL CASES	CASES STUDIED	HEART RATE	AUSCULTATION		JUGULAR PULSE			P WAVES IN ECG		CAROTID SINUS PRESSURE	
						SPLITTING OF SOUNDS	CHANGING INTENSITY OF FIRST SOUND	NORMAL	"CANNON A" WAVES		CONVENT. LEADS	ESOPH. LEADS	ACCEPTED EFFECT	HELPFUL IN THIS SERIES
									REGULAR	IRREGULAR INDEPENDENT				
SUPRAVENTRICULAR	Normal	Sinus tachycardia	>100	10	100–150	N	−	N	+ (If P-R and rate +)	−	+	+	Gradual slowing and return	Seldom at fast rates
		Auric. tachycardia	15	1	125–215	N	−	N	+ (ditto)	−	+	+	Nil, or stops	Nil
		Auric. flutter	32	12	105–190	N	Rare when rhythm abs. regular	N	+ (Rarely striking)	−	±	+	Nil, or abrupt. "Jerky" return	In only 2 cases
		Nodal tachycardia	4	1	110–175	N	−	−	+	−	∓	+	Nil, or stops	Nil
		A-V dissociation	8	1	53–120	N	+	−	−	+	±	+	?	?
	B.B.B.	Sinus tachycardia	10	1	100–150	+	As above	As above	As above	As above	±	+	As above	As above
		Auric. tachycardia	3	1	160–205	+					±	+		
		Auric. flutter	3	2	150–240	+					±	+		
		A-V dissociation	4	1	44–125	+	+	−	−	+	±	+	?	?
VENTRICULAR	Wide QRS	With A-V dissociation	12	6	112–250	++	+	−	−	+	− (Except in 2 cases)	+	Nil	Stopped attack in 1 case
		With auric. fibrillation	5	1	135–210	++	−	N	−	−	−	− (f waves)	Nil	Nil
		With retro. conduction	2	1	110–115	++	−	−	+	−	∓	+	Nil	Nil
		With complete ht. block	3	2	200–220	++	+	−	−	+	∓	+	?	?

usually recorded at normal electrocardiographic speed (25 mm./sec.), but to permit more accurate study, recordings were always made at fast paper speed (75 mm./sec.). The carotid and jugular tracings were obtained by placing a crystal microphone directly on the neck, thus avoiding delay from air conduction.[36]

The components of split first and split second sounds were identified by determining their respective relationship to the onset and nadir of the dicrotic notch of a synchronously recorded right carotid pulse tracing. Tracings taken at high speed were essential for accurate study. Since the dicrotic notch is produced by aortic valve closure it can be used to identify the components of a widely split second sound.[37,38] Thus the component due to aortic valve closure precedes the nadir of the notch by 0.015 to 0.025 second which represents the delay in pulse wave transmission from the aortic valve to carotid artery.[37,39] The component occurring after the dicrotic notch was assumed to be due to pulmonary valve closure, and this was usually confirmed by finding wide splitting of the first sound with earlier ejection from the left ventricle (Figs. 6 and 7).

The onset of the carotid pulse was used to identify the components of a widely split first sound. The major components of the first sound occur at the onset of ventricular systole and are due to mitral and tricuspid valve closure.[33,39] Splitting of the first sound has been shown to be due to ventricular asynchrony resulting in asynchronous closure of the A-V valves.[37,40] The onset of the carotid pulse follows mitral valve closure by a short time interval equivalent to the isometric contraction time of the left ventricle plus the time of pulse wave transmission from the aortic valve to carotid artery (0.015 to 0.025 sec.). Thus, if the onset of carotid pulse falls between two components of a widely split first sound, the first component is related to mitral valve closure and the second to tricuspid closure (Figs. 6 and 7).

In those cases where conventional leads failed to show clear P waves the esophageal electrode was used. The electrode was passed through the nose and down the esophagus and the tube was affixed to the face with Scotch tape, when a suitable site had been selected. The direct-writing Sanborn Visocardiette was used to determine the optimal site of auricular activity. By interchanging the recording instruments, simultaneous sound and esophageal tracings were made. In ventricular tachycardia V_1 and V_6 were always studied to determine from which ventricle the ectopic focus originated. Tracings were taken during and after paroxysms.

The clinical findings were confirmed by these methods.

RESULTS

Seventy-nine cases of paroxysmal tachycardia with regular rhythm have been encountered during the period of study. Of these there were eighteen cases of auricular tachycardia, four of nodal tachycardia, thirty-five of auricular flutter, and twenty-two of ventricular tachycardia. However, only those cases in whom we were able to confirm the clinical findings by simultaneous sound and by jugular venous and electrocardiographic tracings form the basis of this study. Those cases not included showed the same diagnostic clinical features. There were seventeen cases of supraventricular tachycardia and ten cases of ventricular

tachycardia. During the course of the investigation eleven cases of sinus tachycardia were studied in differentiating them from paroxysmal tachycardia. In all cases the heart rate was rapid and regular. The findings are analyzed in Table I.

Carotid sinus pressure was routinely employed but in this series was of little diagnostic value, in fact in one case it was misleading, as it terminated an attack of ventricular tachycardia. Similar difficulties have been experienced.[9] The slight irregularity sometimes present in ventricular tachycardia[21] was of little value in diagnosis as it was usually not detected clinically.[5,41] Moreover, it may occur in supraventricular tachycardia,[41] particularly auricular flutter.

Supraventricular Tachycardia.—In twenty-four of our cases of supraventricular tachycardia auscultation showed single or normally split first and second heart sounds (Figs. 1 to 4). In the majority of cases sound tracings revealed single or broad first sounds and the width of splitting when recorded ranged from 0.02 to 0.04 second. The ECG in all these cases showed a QRS interval of normal duration. In the remaining four cases there was wide splitting of the first (aver. 0.06 second) and second heart sounds (Fig. 6) and in these cases bundle branch block was present. In none of these cases of supraventricular tachycardia with regular rhythm was there alteration in the intensity of the first sound (Figs. 1 to 3, 6). The electrocardiographic counterpart was the finding of a constant P-R interval in each case. We have not included in this series, auricular flutter with slight ventricular irregularity in which the intensity of the first sound varies[42] (Fig. 4). Nor have we included nodal rhythm with retrograde block of the nodal impulses giving rise to A-V dissociation[43,70,71] (Fig. 5), and hence changing intensity of the first sound, as we have not studied such a disturbance with a tachycardia.

In twenty-six of our twenty-eight cases of supraventricular tachycardia inspection of the jugular venous pulse showed no abnormality. In particular, irregular, independent "Cannon A" waves were not seen. The very rapid small "a" waves of auricular flutter were seldom recognized clinically. In the remaining two cases, nodal tachycardia (Fig. 3) and 1:1 auricular flutter (Fig. 6), regular "Cannon A" waves occurring at the same rate as the pulse was a striking clinical feature.

In two cases only, esophageal leads (Figs. 3 and 6) were required to demonstrate auricular activity. For the rest, standard leads showed satisfactory P waves preceding each ventricular complex.

Ventricular Tachycardia.—In all ten cases of ventricular tachycardia wide splitting of the first and second heart sounds was present (Figs. 8, 9, 11). The time interval between the onset of the major high-frequency components of the split first sound averaged 0.08 second, ranging from 0.05 to 0.10 second. The electrocardiogram always showed an abnormally wide QRS complex, the ectopic focus arising from the left ventricle in eight cases. In eight of the ten cases changing intensity of the first heart sound was noted indicating auriculoventricular dissociation (Figs. 8 and 9). In the remaining two the intensity of the first sound remained constant.

In those cases of ventricular tachycardia with varying intensity of the first heart sound, inspection of the jugular venous pulsations revealed irregular, independent "Cannon A" waves (Fig. 7), which were absent in the two cases in whom the first heart sound was constant.

In all cases the conventional leads showed wide QRS complexes and with two exceptions failed to demonstrate auricular activity. It was thus usually impossible to differentiate ventricular tachycardia from supraventricular tachycardia with bundle branch block. The esophageal lead, however, demonstrated clear independent P waves in nine of the ten cases thus establishing the diagnosis (Figs. 8 and 9). In the one case, where extensive search had failed to demonstrate auricular activity, auricular fibrillation was considered to be present and confirmed when the attack subsided (Fig. 11). This case also showed no independent "Cannon A" waves and a constant first heart sound.

Similarly, the first sound did not vary in intensity in the one case of paroxysmal ventricular tachycardia with retrograde conduction.

DISCUSSION

Supraventricular Tachycardia.—

Supraventricular tachycardia with normal ventricular conduction: If auscultation in a case of rapid regular heart action reveals single or closely split heart sounds, the diagnosis of supraventricular tachycardia can be made with confidence. This is dependent on the normal intraventricular conduction (QRS) that is usually present in this disturbance. No matter where the pacemaker arises, whether sinus, nodal, or auricular, the ventricles are stimulated through the normal conducting pathways. The components of the heart sounds therefore maintain a normal relationship to each other and thus gross splitting does not occur (Figs. 1 to 4). Further differentiation of sinus tachycardia, auricular tachycardia, nodal tachycardia, and auricular flutter cannot be made by auscultation alone. Occasionally, however, there is sufficient variation in the first heart sound to suggest auricular flutter,[42] but here the rhythm is usually irregular from varying A-V block (Fig. 4). Variation in the first sound also occurs in nodal tachycardia with retrograde block of the nodal impulses giving rise to A-V dissociation (Fig. 5).

Recognition of "flutter" waves in the jugular venous pulse is difficult and in our experience unreliable. The small "a" waves are presumably due to feeble auricular contraction and at this speed differentiation from the other venous waves is difficult (Fig. 2). On the other hand, regular "Cannon A" waves* at the same rate as the pulse are occasionally encountered in supraventricular tachycardia. "Cannon A" waves occur when the right auricle contracts on a closed tricuspid valve. It is thus found in nodal tachycardia where right auricular contraction follows right ventricular contraction (Fig. 3). It also occurs in very

*We recognize several forms of the "a" wave in the jugular venous pulse. The normal "a" wave is a small presystolic pulsation. When there is right auricular hypertrophy, as in severe pulmonary hypertension, severe pulmonary stenosis and tricuspid stenosis, the "a" wave becomes dominant and even "giant."[67, 68] The "Cannon A" wave, although a striking pulsation, is not dependent on right auricular hypertrophy; it is produced by contraction of the right auricle on a closed tricuspid valve.[69]

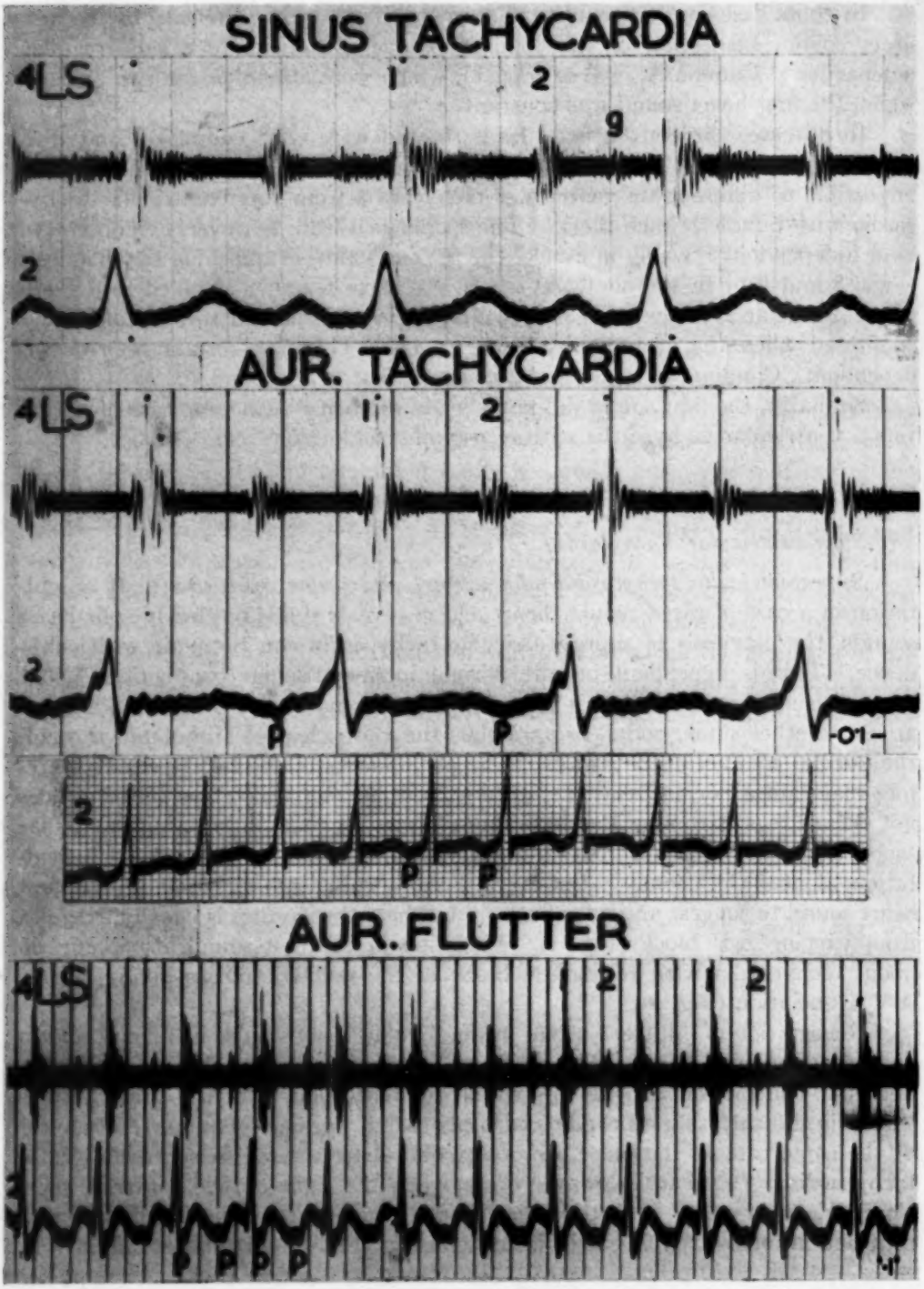

Fig. 1. *(For legend see opposite page.)*

rapid heart rates where the right auricle contracts before the tricuspid valve opens (Fig. 6) and in less rapid rates where prolongation of A-V conduction (prolonged P-R) exists. With the rare exception of nodal tachycardia with retrograde block of the nodal impulses giving rise to A-V dissociation, irregular independent "Cannon A" waves do not occur in supraventricular tachycardia.

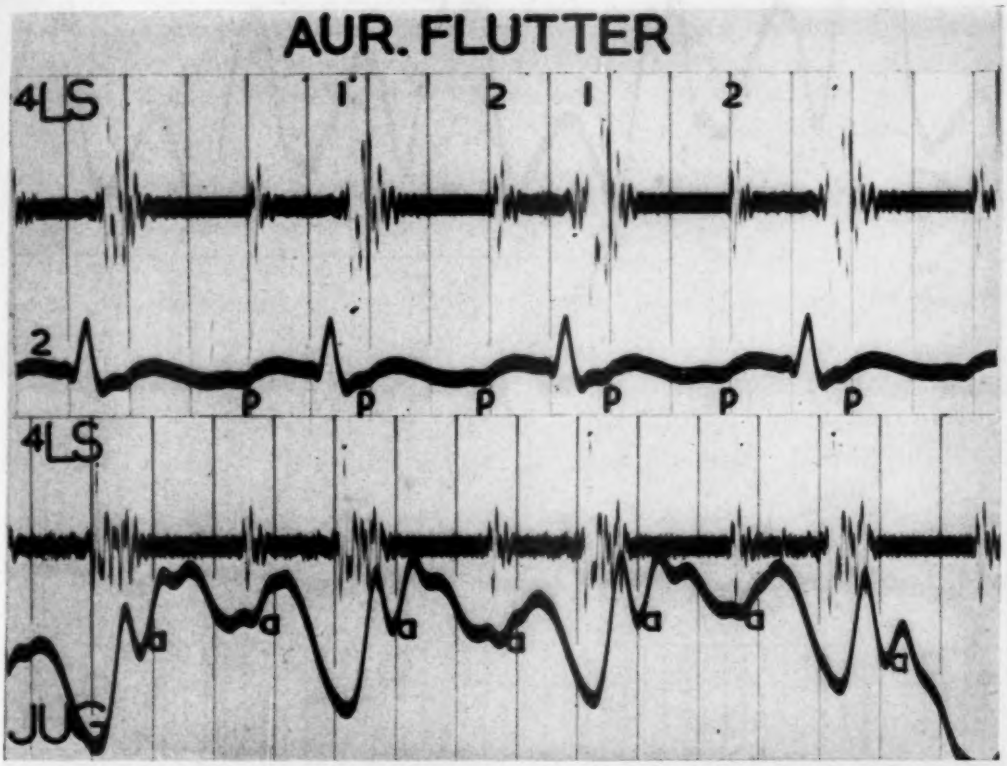

Fig. 2.—Synchronous phonocardiograms at 4LS, Lead II, and jugular venous tracing, respectively, (75 mm./sec.).

PCG, The sounds are not split and thus the diagnosis of supraventricular tachycardia can be made.

ECG, Auricular flutter at 300 with 2:1 block is present. Since the P-R interval is constant, there is no variation in the intensity of the first sound.

JUG, There are small regular "a" waves (*a*) and even those occurring during right ventricular systole are not striking. Flutter could not be recognized clinically by these "a" waves.

Because of the normal QRS complex the conventional electrocardiographic leads establish the diagnosis of supraventricular tachycardia with normal conduction beyond doubt. In most cases P waves are clearly visible in one or other lead and sinus tachycardia, auricular tachycardia, and auricular flutter can be

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Fig. 1.—In all three examples of supraventricular tachycardia, sinus tachycardia, auricular tachycardia, and auricular flutter, the first and second heart sounds (*1,2*) are single or normally split, as there is no abnormal ventricular asynchrony (QRS < 0.10 sec.). There is no variation in the intensity of the first sound, as there is no A-V dissociation. In each instance, the first sound is accentuated because of the tachycardia. The P waves are clearly shown in all three conditions. In sinus tachycardia (rate 120) the P waves and P-R interval are normal. In auricular tachycardia (rate 142) the P waves are inverted and the P-R interval is 0.11 sec. In auricular flutter (rate 290), 2 :1 rhythm is present. Esophageal leads are therefore not required. In the case of sinus tachycardia (due to beriberi heart failure) a summation gallop (*g*) is also recorded. Black dots have been used in this and subsequent figures to show the limits of heart sound vibrations.

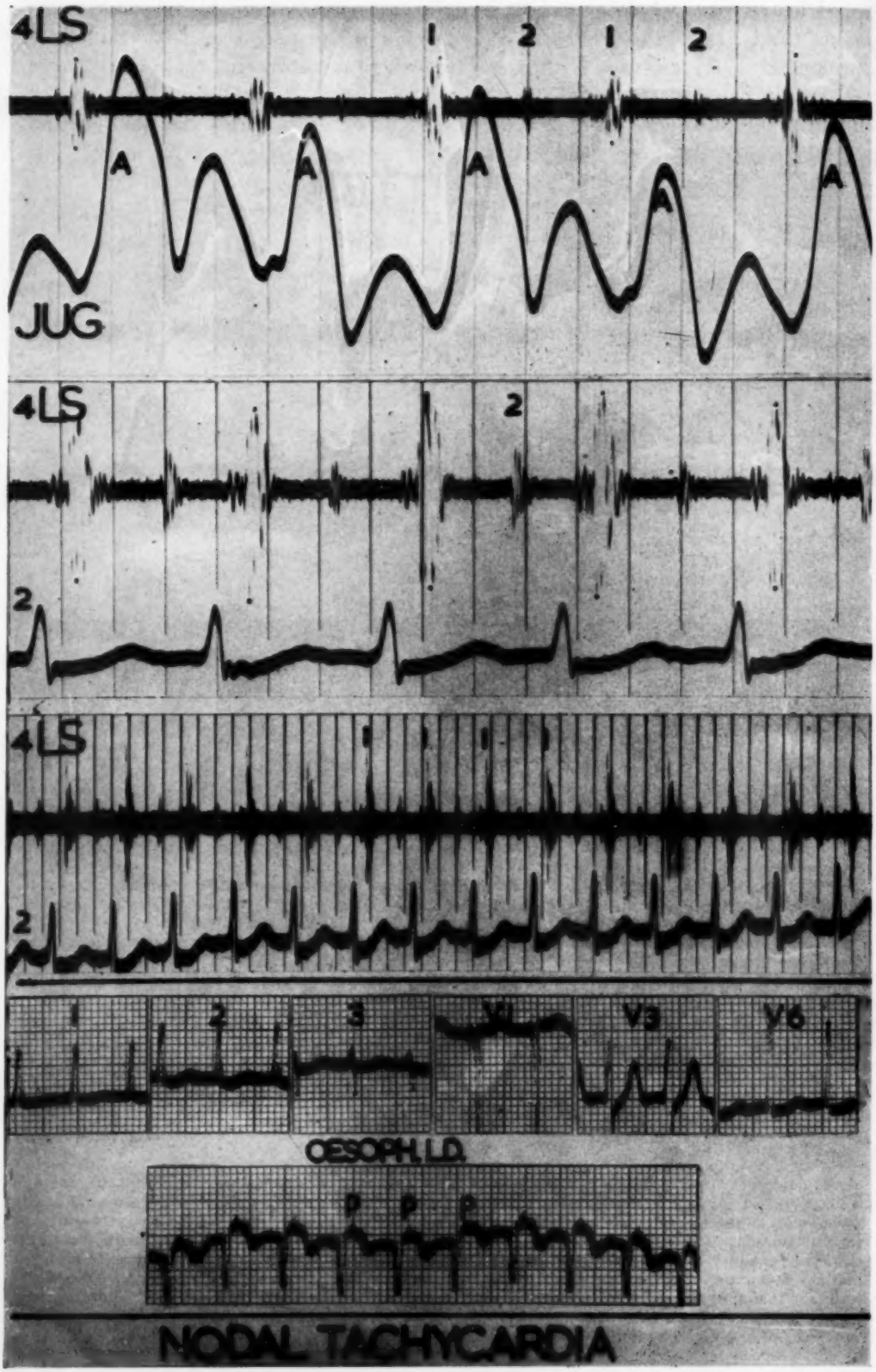

Fig. 3. *(For legend see opposite page.)*

differentiated. In nodal tachycardia where the P waves are buried and obscured by the QRS-T complexes, esophageal leads are invaluable (Fig. 3).

Supraventricular tachycardia with abnormal ventricular conduction: In some cases of supraventricular tachycardia, functional bundle branch block occurs. Moreover, supraventricular tachycardia may occur in a case with established bundle branch block. The resultant ventricular asynchrony produces wide splitting of the heart sounds. However, because there is no A-V dissociation, there is no variation in intensity of the first heart sound and no irregular independent "Cannon A" waves, thus differentiating it from ventricular tachycardia with independent auricular activity (Fig. 6). The value of these bedside signs

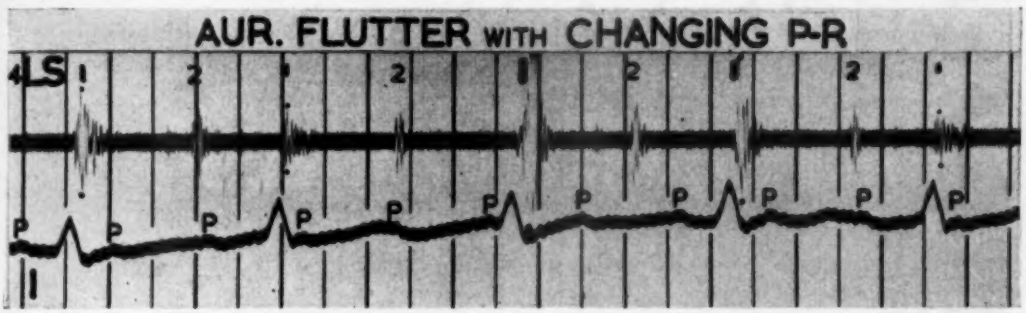

Fig. 4.—Synchronous phonocardiogram at 4LS and Lead I, (75 mm./sec.-reduced). The sounds are closely split and thus the diagnosis of supraventricular tachycardia can be made. The rhythm is slightly irregular (120) due to auricular flutter with varying block. There is a striking variation in the intensity of the first sound, the loud sounds being associated with short P-R intervals and the soft sounds with long P-R intervals.

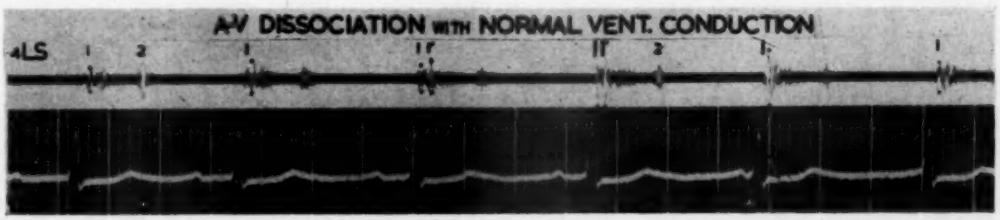

Fig. 5.—Synchronous phonocardiogram at 4LS and Lead I, (75 mm./sec.-reduced). The ECG shows a nodal rhythm of 95 with retrograde block of the nodal impulses, giving rise to A-V dissociation, with an auricular rate of 85. Thus there is variation in the intensity of the components of the first sound. The QRS is normal and the first sound is normally split (1, 1′). It is therefore possible to encounter variation in the first sound in the supraventricular rhythm.

Fig. 3.—This shows a rapid regular tachycardia (170) with normal close splitting of the heart sounds, no variation in the intensity of the first sound and regular "Cannon A" waves (170).

JUG, Synchronous jugular venous tracing and phonocardiogram at 4LS, (75 mm./sec.). Regular "Cannon A" waves (*A*) at the same rate as the ventricles (170) occur during right ventricular systole (*1-2*), due to right auricular contraction on a closed tricuspid valve.

LEAD II, Synchronous phonocardiograms at 4LS and Lead 2, (75 mm./sec. and 25 mm./sec.). The sounds are closely split and thus the diagnosis of supraventricular tachycardia can be made. The normal QRS confirms this diagnosis. There is no significant variation in the intensity of the first sound. The first sound is loud and the second soft due to the tachycardia.

ECG, The conventional leads fail to show P waves.

OES. LD: P waves can be seen following each QRS complex thus confirming the clinical diagnosis of nodal tachycardia.

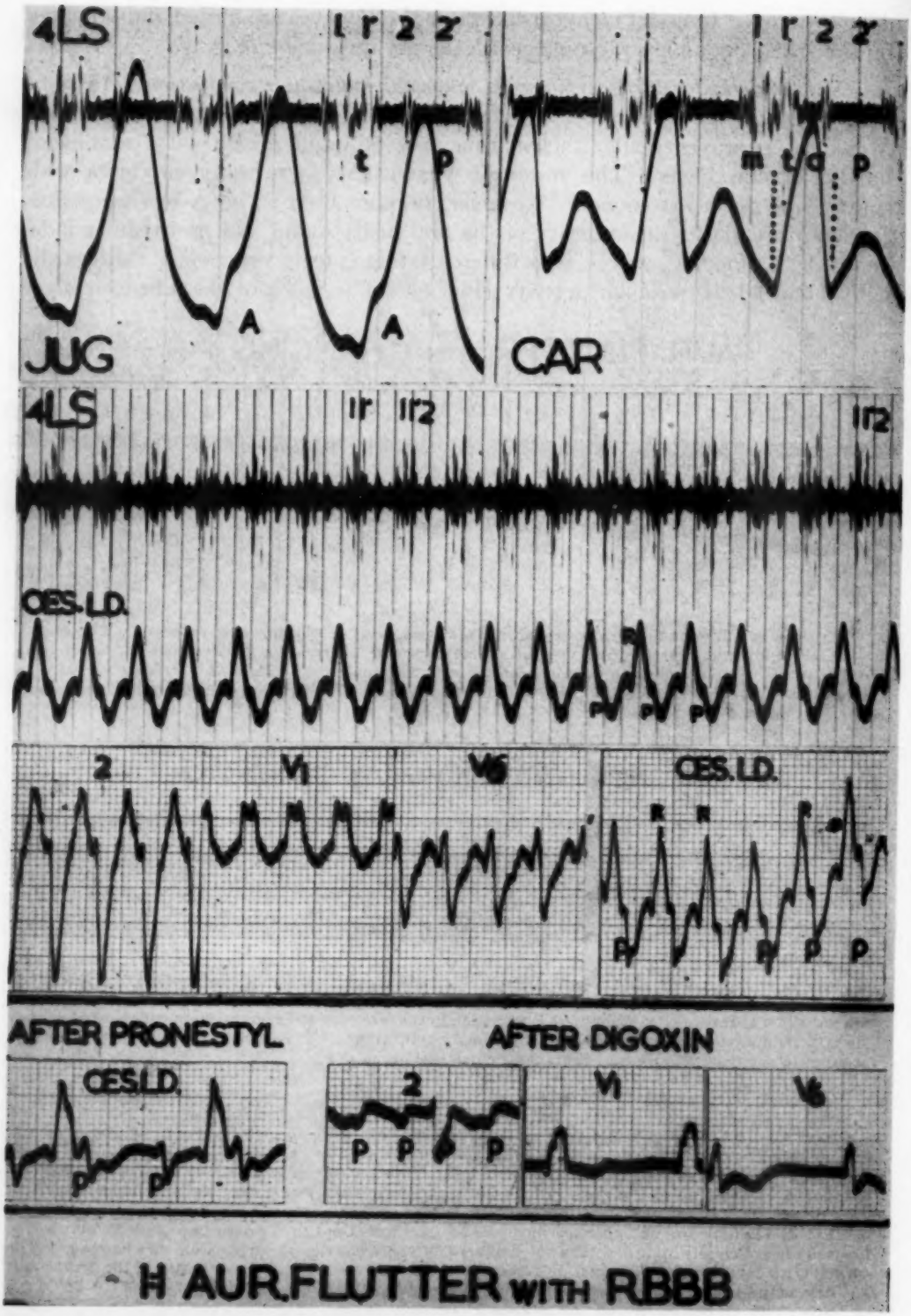

Fig. 6. *(For legend see opposite page.)*

cannot be sufficiently stressed because the conventional ECG leads rarely differentiate supraventricular tachycardia with bundle branch block from ventricular tachycardia; in fact many reported cases of ventricular tachycardia may well be due to the former. Esophageal leads, however, reveal the identical auricular and ventricular rates with a constant P-R interval (Fig. 6).

Similar findings would be anticipated during attacks of supraventricular tachycardia in cases with the Wolff-Parkinson-White syndrome.[44] During such an attack the QRS may develop an even greater degree of aberration, but we have not been able to study our cases during an attack.

Ventricular Tachycardia.—

Ventricular tachycardia with independent auricular activity: If auscultation in a case of rapid regular heart action reveals wide splitting of the heart sounds, variation in the intensity of the components of the first sound and independent, irregular "Cannon A" waves in the jugular venous pulse, the diagnosis of ventricular tachycardia can be made with confidence. There is only one rare exception which is discussed later.

The rapid and clinically regular discharge of impulses from an ectopic focus in one or other ventricle is the fundamental cause of ventricular tachycardia.[45] Gross asynchronous contraction of the two ventricles is thus produced. The major components of the first heart sound are thought to be due to closure of the mitral and tricuspid valves. Aortic and pulmonary valve closure are mainly responsible for the second sound.[39] The slight ventricular asynchrony that occurs normally in health[37,47,48] is sufficient to produce slight but definite splitting of the heart sounds.[33,37,40,49] In bundle branch block,[37,50] especially right bundle branch block, it is common to find splitting of the heart sounds which is due to

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Fig. 6.—There is wide splitting of both heart sounds due to ventricular asynchrony. There is no variation in the intensity of the first sound and no irregular, independent "Cannon A" waves, as there is no A-V dissociation.

***CAR*, Synchronous carotid tracing and phonocardiogram at 4LS, (75 mm./sec.). Due to ventricular asynchrony both sounds are widely split (1, 1′; 2, 2′). The onset and dicrotic notch of the carotid pulse identify the components of the split sounds (for details see Fig. 7), showing that left ventricular systole (*m-a*) precedes right ventricular systole (*t-p*).**

***JUG*, Synchronous jugular venous tracing and phonocardiogram at 4LS, (75 mm./sec.). Regular "Cannon A" waves (*A*) of equal force, at the same rate as the ventricles (220) occur during right ventricular systole (*t-p*). Right ventricular contraction on a closed tricuspid valve (*t*) thus produces these giant "A" waves.**

***OES. LD*, Synchronous phonocardiogram at 4LS and esophageal lead, (25 mm./sec.). The sound tracing shows wide splitting but no variation in the intensity of the components of the first sound. The esophageal lead confirms the absence of A-V dissociation, the P waves (*p*) being clearly shown at the same rate as the QRS complexes (*R*). The first sound is grossly accentuated, whereas the second is diminished due to the tachycardia. The asynchrony is shown by the widened QRS of 0.13.**

***ECG*, Leads II, V_1 and V_6 show a regular tachycardia (220) with widened QRS (0.13), but no evidence of auricular activity, hence supraventricular tachycardia with bundle branch block cannot be distinguished from ventricular tachycardia. Esophageal lead clearly demonstrates P waves (*P*) at the same rate as the QRS complexes (*R*), thus the diagnosis is narrowed down to supraventricular tachycardia with bundle branch block and ventricular tachycardia with retrograde conduction, confirming the clinical diagnosis.**

***PRONESTYL* (0.9 mg. i.v.). *OES. LD*, The development of 2:1 A-V block proves that the disturbance above was supraventricular tachycardia (flutter) with bundle branch block. The Pronestyl has slowed the auricular rate to 140, prolonged the P-R interval from 0.14 to 0.25, and widened the QRS to 0.16.**

***DIGOXIN*, (1.5 mg.). Leads II, V_1 and V_6 show auricular flutter (2:1) with right bundle branch block. When sinus rhythm was ultimately restored the right bundle branch block persisted.**

ventricular asynchrony of a magnitude greater than that in health. We believe that the greatest asynchrony of all may occur in ventricular premature systoles and ventricular tachycardia. If, for example, the ectopic focus arises in the free

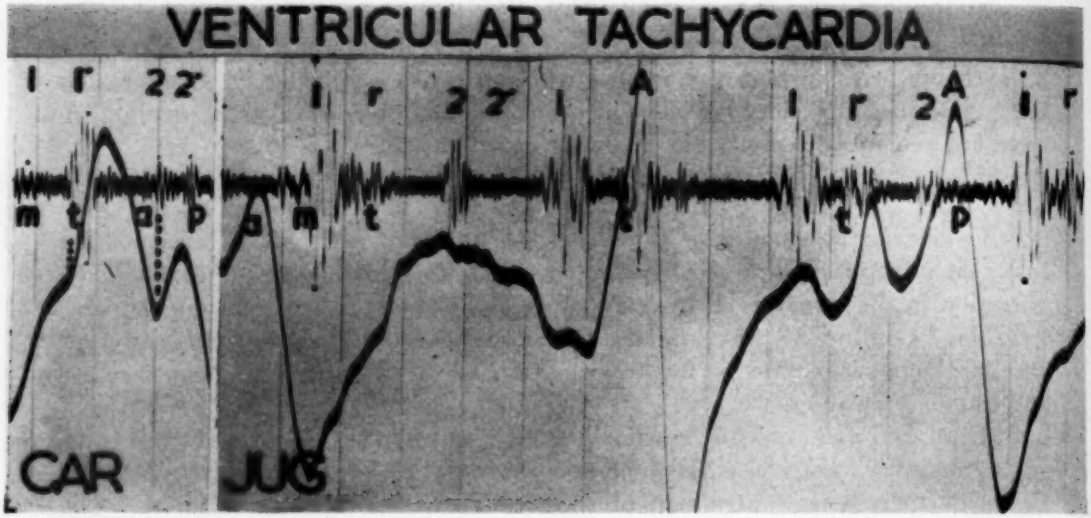

Fig. 7.—*CAR*, Synchronous carotid tracing and phonocardiogram at 3LS, (75 mm./sec.). Due to ventricular asynchrony both sounds are widely split (1, 1′; 2, 2′). The onset of the carotid pulse identifies each component of the split first sound. The first component (*1*) must be due to mitral valve closure (*m*) as the second component (*1′*) occurs after the onset and therefore can only be due to tricuspid valve closure (*t*). The component (*2*) occurring at the dicrotic notch is produced by aortic valve closure (*a*). The component (*2′*), occurring after the dicrotic notch cannot be due to aortic valve closure and is due to pulmonary valve closure (*p*). Thus left ventricular systole precedes right ventricular.

JUG, Synchronous jugular venous tracing and phonocardiogram at 4LS, (75 mm./sec.). This tracing illustrates the effect of A-V dissociation on the intensity of the mitral and tricuspid components of the first sound. There is varying intensity of each component of the split first sound depending on the relation of the auricular contraction (*a*,*A*) to mitral (*m*) and tricuspid valve (*t*) closure, respectively. Left and right auricular systole are assumed to be virtually synchronous, so that *a-t* (and *A-t*) measures the P-R interval on the right side and *a-m* (*A-m*) measures the P-R interval on the left. In the first cycle there is a loud mitral component (a-m = 0.16) and a soft tricuspid (a-t = 0.25). In the second cycle the tricuspid component is very loud (A-t = 0.06) whereas in the fourth it is soft (A-t = 0.22). In the third cycle both the tricuspid and mitral components are soft as there is no auricular contraction during the preceding diastole. Similarly, the mitral component is soft in the second cycle, whereas it is loud in the fourth (A-m = 0.12). The effect of A-V dissociation on the jugular venous pulse is also shown. In the first cycle there is a normal "a" wave (*a*) preceding tricuspid valve closure; in the second there is a large "Cannon A" wave (*A*) due to almost synchronous contraction of right auricle and right ventricle, the right auricle contracting on a closing tricuspid valve. In the third cycle a smaller "Cannon A" wave (*A*) is revealed because right auricular contraction occurs at the end of right ventricular systole (*t-p*), the tricuspid valve opening during the end of right ventricular systole. The variation in size of the "Cannon A" waves, their independence, and irregularity are thus demonstrated.

Fig. 8.—4LS, Synchronous phonocardiogram at 4LS and Lead I, (75 mm./sec.). The sound tracing shows wide splitting of both heart sounds (1, 1′; 2, 2′). There is a striking independent variation in intensity of each component of the split first sound. The ECG shows a wide QRS of 0.18 but no evidence of auricular activity.

MA, Synchronous phonocardiogram at *MA* and esophageal lead, (75 mm./sec.). The sound tracing shows wide splitting (0.09) and variation in intensity of the first sound. The ECG shows independent P waves. The intensity of each component of the first sound varies according to its respective P-R interval.

ECG, The conventional leads show a regular tachycardia of 170. The QRS is wide (0.18), but no P waves are visible and thus the diagnosis of ventricular tachycardia cannot be established. The ectopic focus arises from the left ventricle. The esophageal lead shows the independent slower auricular rate of 120 with the ventricular rate of 170. The clinical diagnosis of ventricular tachycardia with independent auricular action is thus confirmed. Figs. 7 and 8 were taken from the same patient.

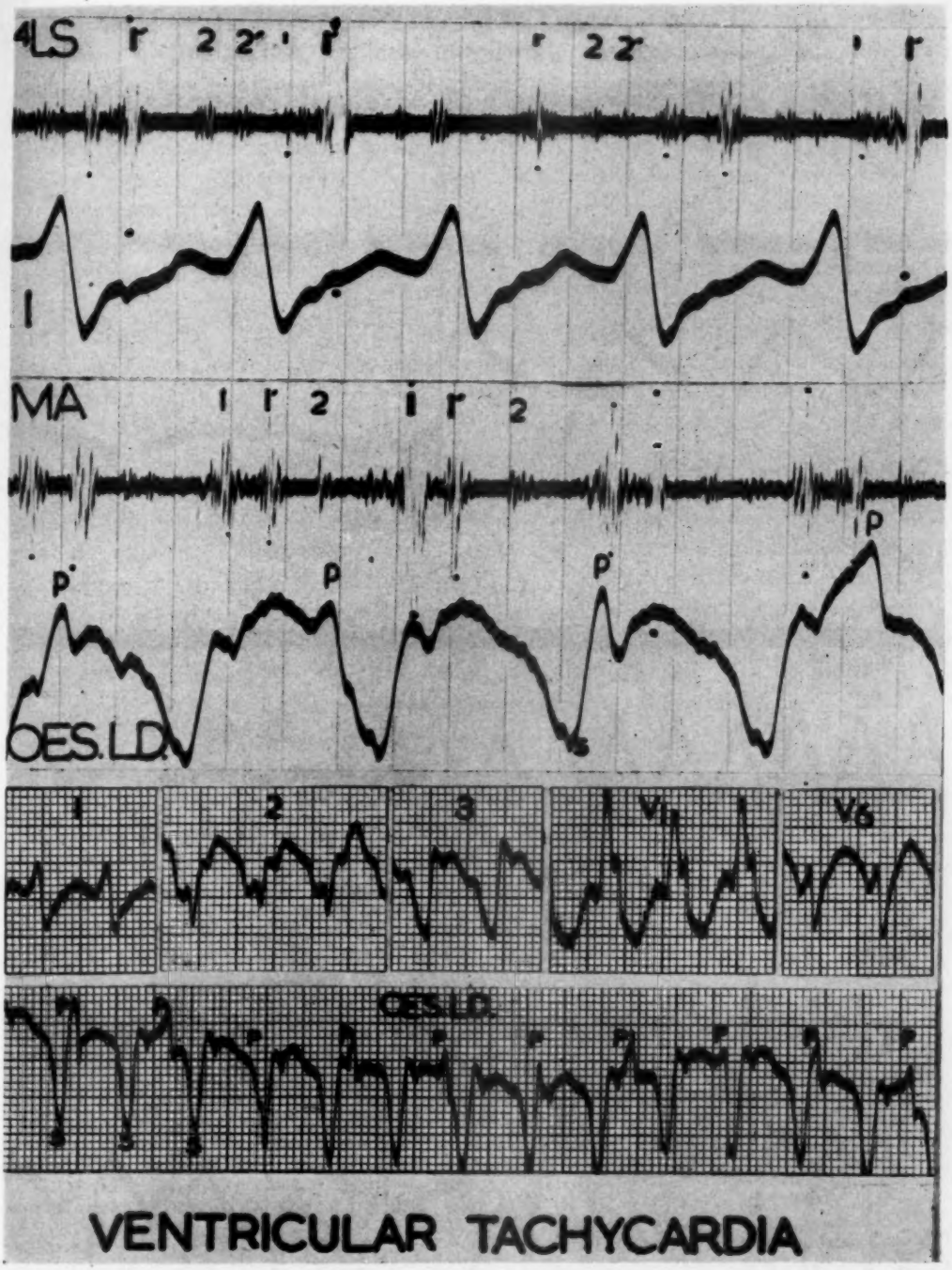

Fig. 8. *(For legend see opposite page.)*

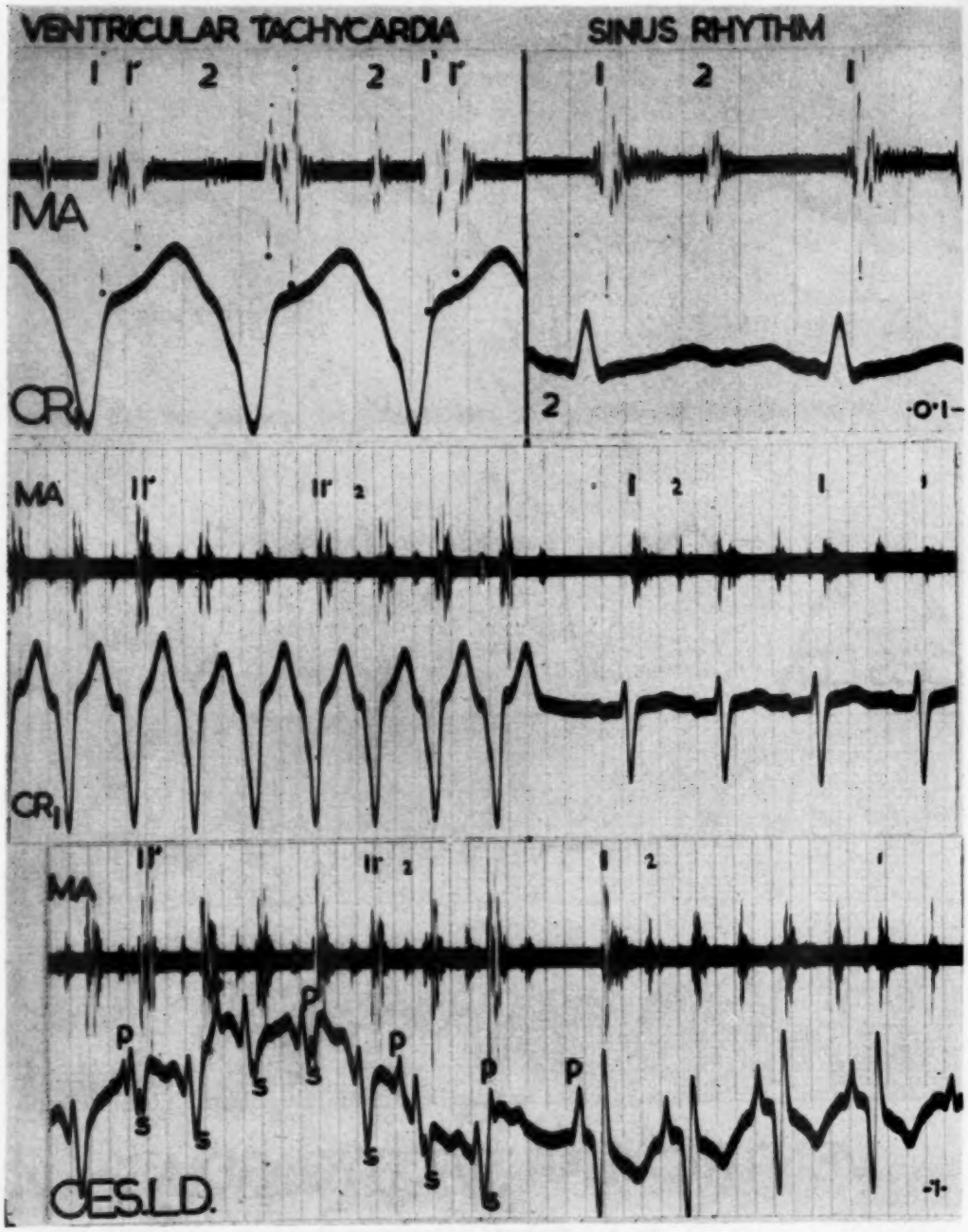

Fig. 9. *(For legend see opposite page.)*

wall of the left ventricle there is marked delay in activation of the right ventricle as shown by the wide QRS interval. Thus, the most striking auscultatory feature of ventricular tachycardia is the gross degree of splitting of the heart sounds which contrasts sharply with the single or closely split sounds found in supraventricular tachycardia with normal ventricular conduction. This difference in the degree of splitting is easily recognized at fast rates (Figs. 1 and 9), and its importance in the differentiation of ventricular tachycardia from supraventricular tachycardia with normal conduction has not been hitherto described.

Splitting of the heart sounds must be sought for in the appropriate positions. Thus, splitting of the first sound is best heard at the mitral area and lower left sternal edge.[33,51,52,54] Splitting of the second sound, on the other hand, is best heard at the pulmonary area and the third left intercostal space, but not in the mitral and aortic areas, because the normal pulmonary component is not conducted to these areas.[38,55,56] In tachycardia, the first sound is grossly accentuated (Figs. 1 to 3, 6 to 9, 11), because with the shortened diastole the A-V valves are still wide apart at the onset of ventricular systole.[42] The second sound, on the other hand, becomes diminished, at times markedly so, dependent on the fall in cardiac output and blood pressure with increasing heart rate.[1,57] In consequence, splitting of the first sound in ventricular tachycardia is far more readily appreciated than splitting of the second sound. In fact the second sound may be inaudible, and the heart rate misinterpreted as being one-half the actual rate.[1] Moreover, if the patient is pulseless and the blood pressure unobtainable, the diagnosis of tachycardia may be completely missed. Wide splitting of the first sound (Fig. 11) may afford the only clinical clue to the diagnosis.

As a rule, in ventricular tachycardia (eight of ten cases) the auricles contract quite independently of the ventricles, and the two chambers are thus dissociated, the ventricles contracting faster than the auricles (Figs. 7 to 9). It is this dissociation between auricles and ventricles that is responsible for the variation in intensity of the first heart sound. The position of the auriculoventricular valves at the commencement of systole is the important factor in determining the intensity of the first sound.[42,58,59] and is related to the P-R interval. In ventricular tachycardia, the P-R interval is constantly changing, and in consequence there is varying intensity of the first sound.[20]

Fig. 9.—Synchronous phonocardiogram at MA and Lead CR_1, (75 mm./sec.). At this site wide splitting (0.05) of the first sound only is recorded. The splitting is not as gross as that shown in Fig. 8 because the QRS measures only 0.11 as compared with 0.18 sec. However, the width of splitting even with a QRS of 0.11 is noteworthy. The ECG shows a heart rate of 200 with the ectopic focus arising in the right ventricle.

Synchronous phonocardiogram at MA and Lead II, (75 mm./sec.). The first sound has become single indicating supraventricular tachycardia. The ECG shows sinus tachycardia of 130 with a QRS of 0.08.

Synchronous phonocardiogram at MA and Lead CR_1, (25 mm./sec.). During the paroxysm of tachycardia, there is a wide splitting of the first heart sound with variation in the intensity of each component, indicating ventricular tachycardia with independent auricular activity. The paroxysm ends abruptly, and after a compensatory pause sinus rhythm is restored. The wide splitting disappears and a short systolic murmur is recorded. The intensity of the first sound diminishes progressively as the rate slows.

Synchronous phonocardiogram at MA and esophageal lead, (25 mm./sec.). The sound tracing shows essentially the same features as above during another paroxysm. The ECG confirms the clinical diagnosis of ventricular tachycardia with independent auricular activity (auricular rate, 120; ventricular, 180).

Because of the ventricular asynchrony, the P-R interval on the right side of the heart must differ considerably from that of the left side. As the intensity of the mitral and tricuspid components of the first heart sound each depends on its own P-R interval, variation of the P-R interval will result in variation in the intensity of each component of the widely split sound. Thus the variation of the first sound in ventricular tachycardia is due to independent variation in intensity of the mitral and tricuspid components of the widely split sound (Figs. 7 to 9).

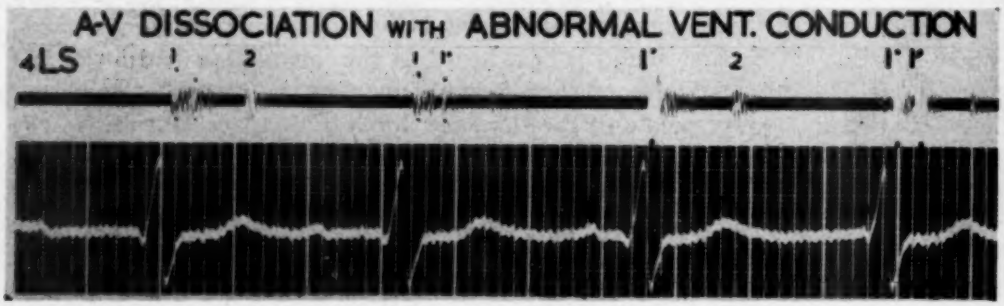

Fig. 10.—Synchronous phonocardiogram at 4LS and Lead I, (75 mm./sec. reduced). The ECG shows a nodal rhythm of 95 with retrograde block of the nodal impulses giving rise to A-V dissociation with an auricular rate of 80. Thus there is variation in intensity of the components of the first sound. The QRS is wide (0.12) and the first sound is widely split (1, 1'). It is therefore possible to encounter variation in intensity and wide splitting of the first sound in a supraventricular rhythm.

Of the two auscultatory phenomena, wide splitting is more easily recognizable than variation in the intensity of the first sound, particularly at fast rates. The former is a reflection of ventricular asynchrony, the latter of auriculoventricular dissociation (Fig. 15).

In ventricular tachycardia with independent auricular activity, inspection of the jugular veins reveals independent, irregular "Cannon A" waves. This was pointed out as long ago as 1920 by Leon Gallavardin. "Cannon A" waves are produced by right auricular contraction on a closed tricuspid valve. The independence of the "Cannon A" waves is due to the varying relationship between auricular and ventricular contractions. Moreover, as the auricular rate is slower than the ventricular, auricular contraction on a closed tricuspid valve occurs irregularly. Variation in the force of the "Cannon A" waves also occurs, depending on the position of the tricuspid valve during auricular systole. Thus when the tricuspid valve is closed throughout right auricular systole, a large wave is produced, whereas when the valve is closed during part of auricular systole, the "Cannon A" wave is smaller (Fig. 7).

By careful clinical examination A-V dissociation was readily detected in every case, whereas in only two of our ten cases were P waves visible in the conventional leads of the electrocardiogram. These leads therefore usually fail to distinguish ventricular tachycardia from supraventricular tachycardia with bundle branch block. A widened QRS complex may thus occur in supraventricular and ventricular tachycardia but auriculoventricular dissociation occurs in ventricular tachycardia alone. To demonstrate this crucial finding electrocardiographically, esophageal leads are essential. We were thus able to prove all our cases of

ventricular tachycardia conclusively (Figs. 8, 9, 12). The extremely rare condition of nodal tachycardia with retrograde block of the nodal impulses giving rise to A-V dissociation has been described by Langendorf,[43] together with bundle branch block. This gave rise to a rapid ventricular rate, prolonged QRS complex, and a slower independent auricular rhythm. Differentiation from paroxysmal

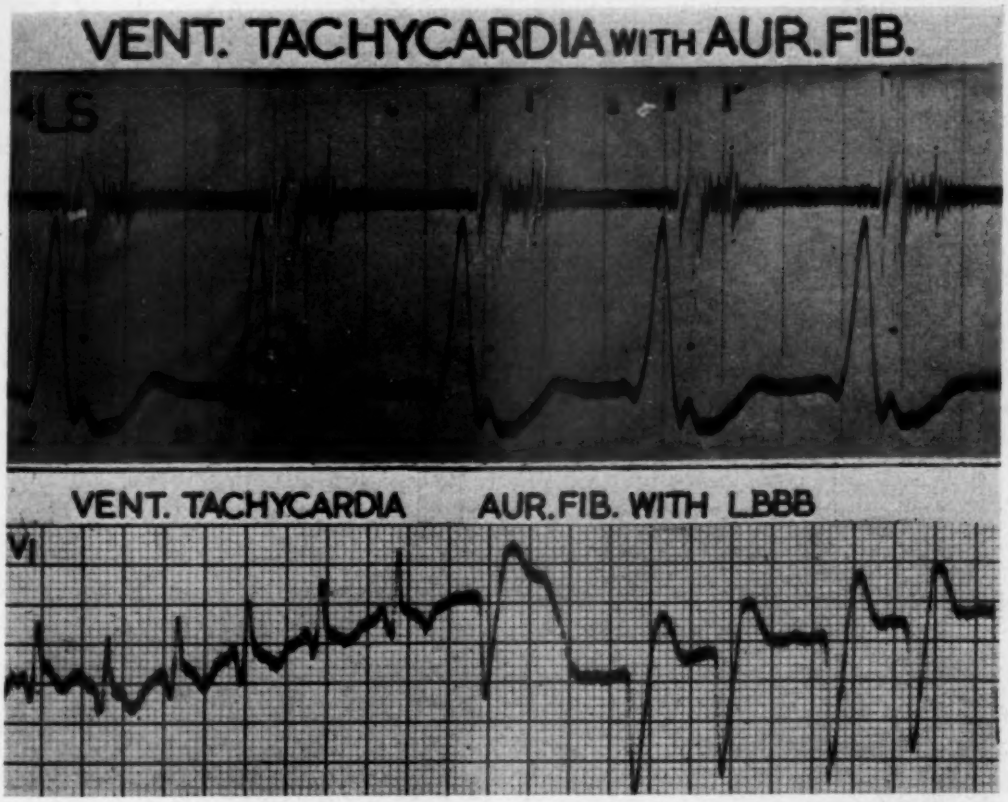

Fig. 11.—Synchronous phonocardiogram at 4LS and Lead II, (75 mm./sec.). The tracing shows a rapid regular tachycardia of 175 with wide splitting (0.9) of the first heart sound but no variation in the intensity of each component. The second sound (2) is markedly diminished due to circulatory collapse and in fact was inaudible clinically. *ECG: (25 mm./sec.)* This shows the termination of a paroxysm of ventricular tachycardia (175) in the same case (ectopic focus in left ventricle) revealing auricular fibrillation with left bundle branch block. The absence of effective auricular activity during the paroxysm (confirmed by esophageal lead) accounts for the unvarying first sound.

ventricular tachycardia with independent auricular rhythm could only be made because of the presence of interference. A-V dissociation is a common finding (Figs. 5 and 10), but its occurrence at a rate comparable to that of the tachycardias must be rare[70] and its association with bundle branch block even more unusual.

Ventricular tachycardia with auricular fibrillation: If auscultation in a case of rapid heart action reveals wide splitting of the heart sounds but no evidence of variation of the first sound and no "Cannon A" waves in the neck this condition must be considered. It must be differentiated from supraventricular tachycardia

with bundle branch block and from paroxysmal ventricular tachycardia with retrograde conduction to the auricles.

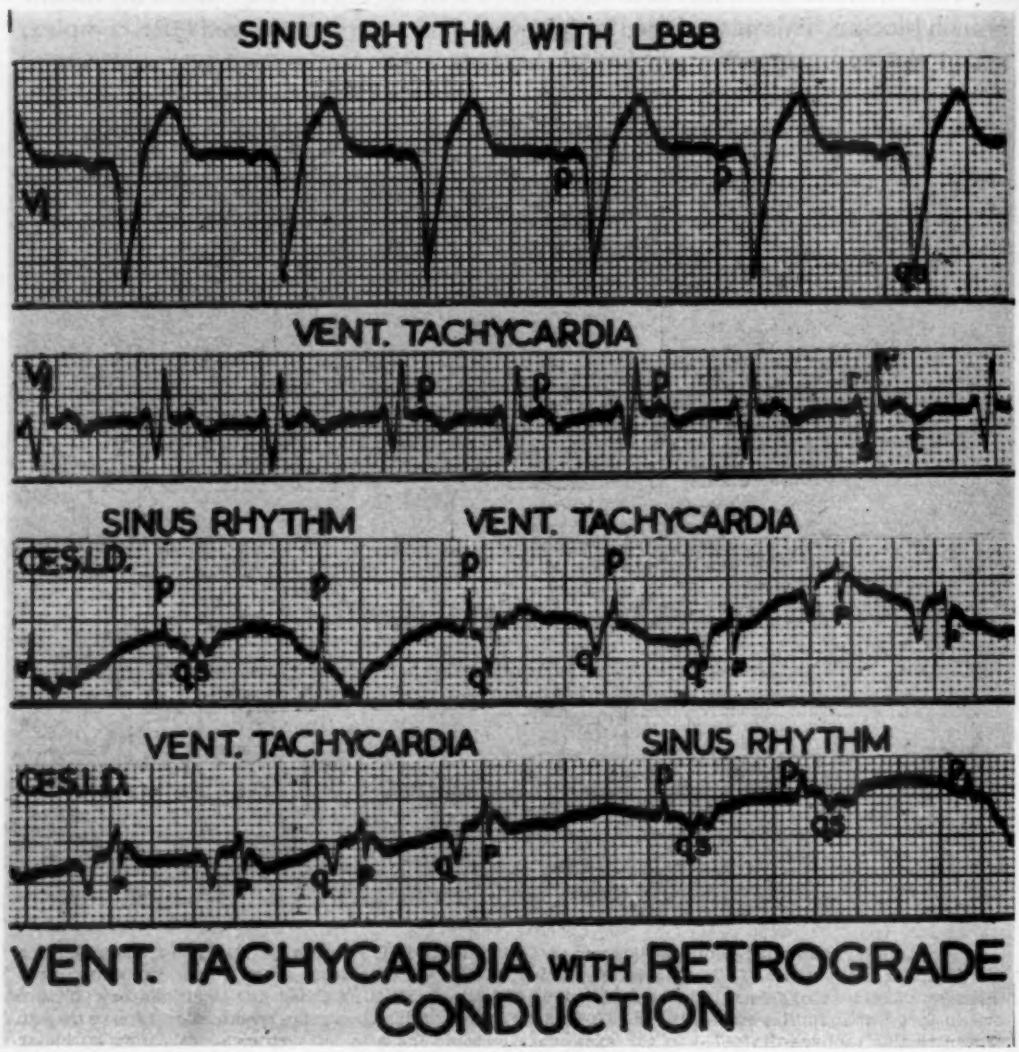

Fig. 12.—The first tracing (V_1) shows sinus rhythm of 78 with left bundle branch block. The second tracing (V_1) shows ventricular tachycardia at 105. The P waves are shown superimposed on the S-T segments. The ectopic focus arises in the left ventricle. The third tracing (esophageal lead) shows the onset of a paroxysm of ventricular tachycardia. During sinus rhythm the auricular rate is 80; during the ventricular tachycardia (112) the auricular rate suddenly rises to 112 and the auricular complexes clearly alter in configuration, due to retrograde conduction. The first two ventricular ectopic beats do not disturb the sinus rhythm as the impulses reach the A-V node while it is still refractory. The fourth tracing shows the offset of a paroxysm. The last ventricular ectopic beat ends with a retrograde P wave, and after a pause sinus rhythm is restored. All the tracings are taken from the same patient and prove paroxysmal ventricular tachycardia with retrograde conduction to the auricles.

If P waves cannot be found after extensive and careful exploration with the esophageal electrode, auricular fibrillation should be suspected.[60] The diagnosis can be confirmed when the paroxysm ceases (Fig. 11).

Ventricular tachycardia with retrograde conduction to the auricles: In rare

cases of ventricular tachycardia, retrograde conduction to the auricles occurs, resulting in auricular contraction at the same rate as the ventricular.[61] Thus, auriculoventricular dissociation does not occur. We have studied one case in our series.

On auscultation, wide splitting of the heart sounds was present from ventricular asynchrony, but there was no variation in the intensity of the first sound,

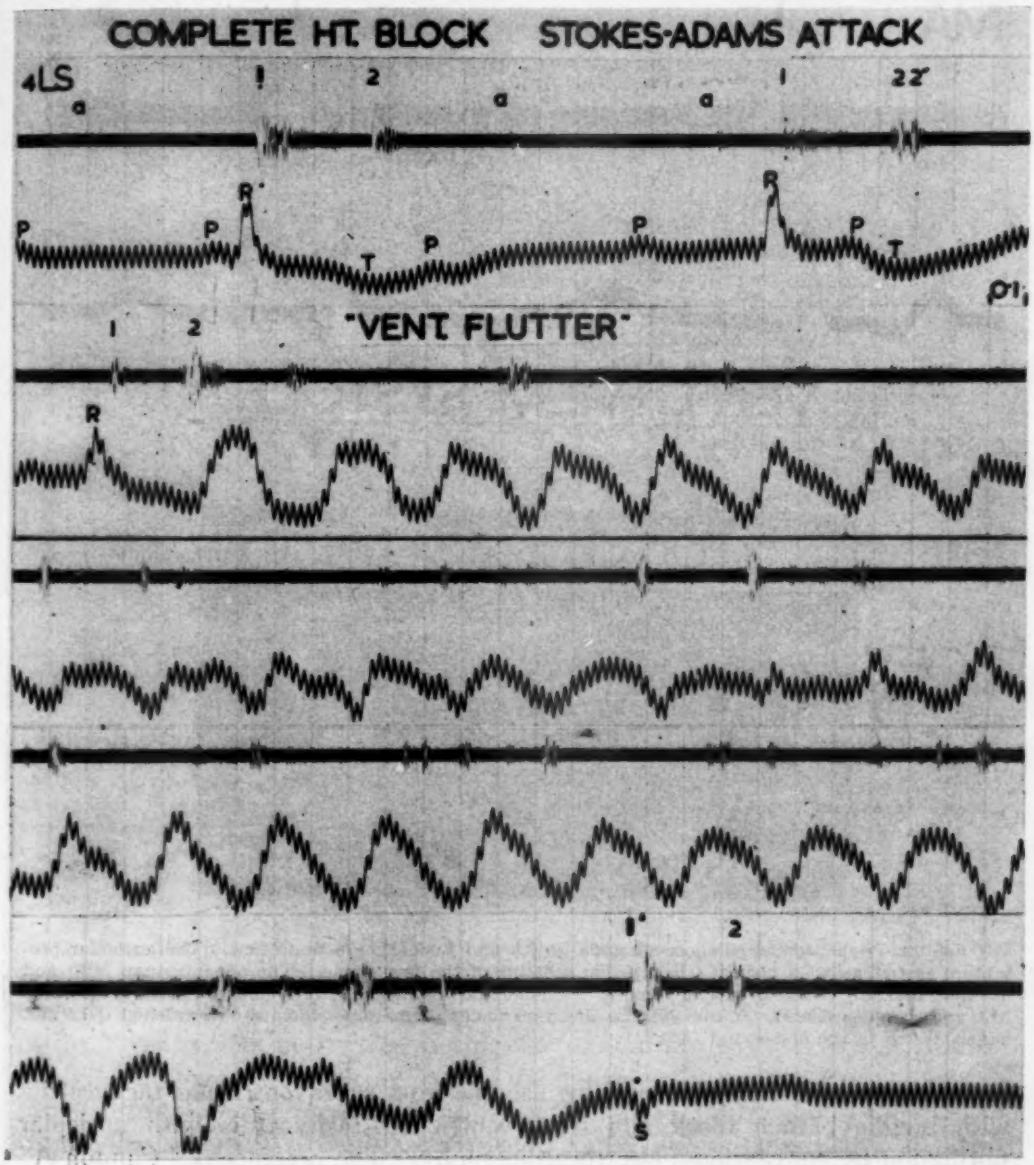

Fig. 13.—Synchronous phonocardiogram at 4LS and Lead II, (75 mm./sec.-reduced). The continuous tracing records the onset and recovery from a Stokes-Adams attack in a case of complete heart block. In the first strip, the characteristic findings of complete heart block are shown. There is varying intensity of the first sound and audible independent auricular sounds (*a*). During "ventricular flutter" syncope was present and definite sounds are recorded. These are irregular and very soft, unlike the loud sounds of ventricular tachycardia. The last strip shows resumption of normal ventricular activity with return of loud sounds. The ECG is disturbed by A-C interference.

indicating the absence of auriculoventricular dissociation. Similarly independent, irregular "Cannon A" waves were not seen. Regular "Cannon A" waves would be expected and have been recorded,[61] but jugular venous tracings were not taken in this case.

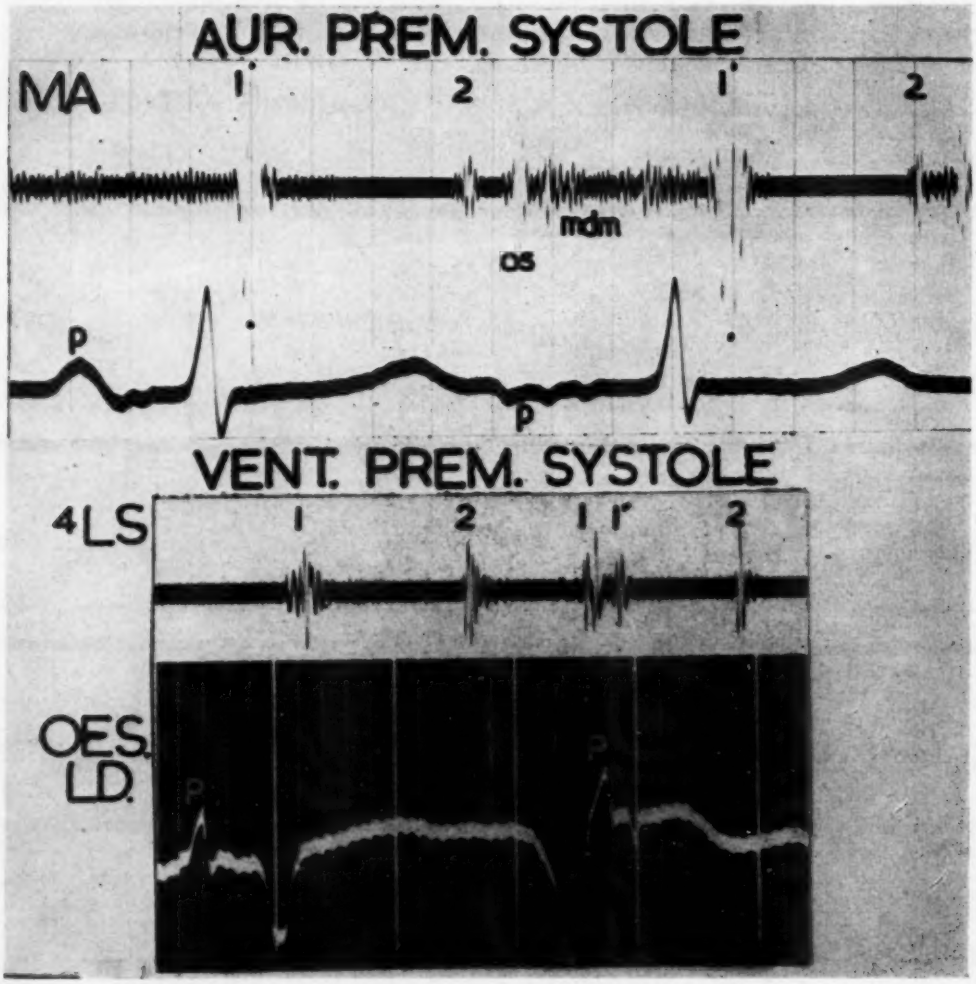

Fig. 14.—Synchronous phonocardiogram at PA and Lead II, (75 mm./sec.). The auricular premature systole shows a normal QRS and no splitting of the first sound. The opening snap (*OS*) and diastolic murmur (*mdm*) of mitral stenosis are incidental findings. Synchronous phonocardiogram at MA and esophageal lead, (75 mm./sec.). The ventricular premature systole shows widened QRS and wide splitting of the first sound (1, 1').

This condition may be indistinguishable from supraventricular tachycardia with bundle branch block and from ventricular tachycardia with auricular fibrillation by conventional electrocardiography. The presence of "Cannon A" waves and the demonstration of auricular activity by the esophageal leads excludes the latter condition but still fails to differentiate ventricular tachycardia with retrograde conduction from supraventricular tachycardia with bundle branch block (Fig. 6). Observation of the relation of the P wave to the QRS at the onset or the offset of the attack affords conclusive proof,[24] and this is best

recorded by the esophageal leads (Fig. 12). Thus, in the case of supraventricular tachycardia with bundle branch block, the diagnosis was established by recording the development of auriculoventricular block during procaine amide administration (Fig. 6). When sinus rhythm was ultimately restored the bundle branch block persisted, each ventricular complex being preceded by a normal P wave. In the case of ventricular tachycardia with retrograde conduction, a right bundle branch block pattern was present during the attack and left bundle branch block when sinus rhythm was restored. Also the onset and offset of the attack clearly demonstrated the ventricular origin of the tachycardia (Fig. 12). This case is being reported in detail elsewhere.

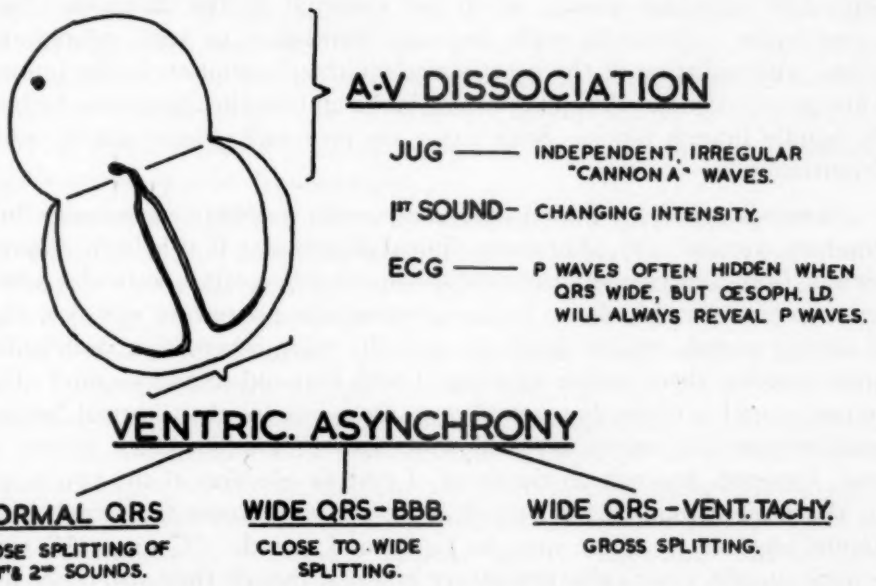

Fig. 15.—The diagram lists the signs by which A-V dissociation and ventricular asynchrony may be recognized. If both A-V dissociation and abnormal ventricular asynchrony are absent the tachycardia is supraventricular in origin. If both are present the tachycardia is almost always ventricular. If abnormal ventricular asynchrony occurs in the absence of A-V dissociation then supraventricular tachycardia with bundle branch block is likely to be present, but ventricular tachycardia with retrograde conduction to the auricles will have to be excluded.

Ventricular tachycardia in complete heart block: We have observed two cases with this disturbance and have included them for completeness. There are several mechanisms whereby Stokes-Adams seizures may be produced in cases of high grade heart block.[62,65] Thus ventricular standstill, ventricular tachycardia, "ventricular flutter" or ventricular fibrillation may be present, respectively. All these conditions occurred at different times in our two cases. Auscultation during a seizure revealed no heart sounds in ventricular fibrillation or ventricular standstill. During ventricular tachycardia (particularly in short bursts) the auscultatory findings were as described in paroxysmal ventricular tachycardia with independent auricular activity. During "ventricular flutter" feeble but definite heart sounds were heard irregularly (Fig. 13), confirming the findings reported by Levine and Harvey,[42] in contrast to the loud sounds of ventricular tachycardia, and the absence of sounds in ventricular fibrillation.[42,63]

In conclusion, in ventricular tachycardia, ventricular asynchrony is always present and independent auricular activity is usually present. The diagnosis can readily be made by bedside auscultation, as there is wide splitting of both the first and second sounds (reflecting the asynchrony), which is readily appreciated, and variation in the intensity of the first heard sound (reflecting the A-V dissociation), which is not as easily detected. The finding of independent, irregular "Cannon A" waves in the jugular venous pulse (reflecting the independent auricular activity), confirms the diagnosis of ventricular tachycardia. The electrocardiogram shows the wide QRS of ventricular asynchrony in the conventional leads, but esophageal exploration is usually necessary to reveal the independent auricular waves, which are essential to the diagnosis (Fig. 15). In ventricular tachycardia with auricular fibrillation or with retrograde conduction, wide splitting of the heart sounds without variation in the intensity of the first sound occurs. A similar finding is encountered in supranodal tachycardia with bundle branch block. Such cases are rare and require special study for differentiation.

Premature systoles: Paroxysmal tachycardia is merely a successive burst of premature systoles.[5,45,66] The same clinical phenomena that help to differentiate auricular from ventricular tachycardia help to differentiate auricular from ventricular premature systoles. In supraventricular premature systoles, the first and second sounds remain single or normally split, whereas in ventricular premature systoles, there is wide splitting of both first and second sounds[37] (Fig. 14). The first sound is often, but not always, more intense than normal because the auriculoventricular valves are still wide apart. The intensity of the second sound, however, depends on the force of systolic ejection of the two ventricles, thus the more premature the ectopic beat, the less intense the sound, in fact in extreme prematurity there may be no second sound. "Cannon A" waves in the neck suggest ventricular premature systoles, though they also occur in nodal premature systoles, which are less common. The "Cannon A" waves may actually produce the symptoms of throbbing in the neck so often complained of by the patient.

Thus it is often possible to diagnose supraventricular and ventricular premature systoles with some confidence by auscultation and inspection of the jugular venous pulse.

SUMMARY

1. The differentiation of a supraventricular from ventricular tachycardia can usually be made by careful bedside auscultation, if particular care is paid to splitting of the heart sounds.

2. In a case of rapid regular tachycardia, if the first and second sounds are single or normally split, the diagnosis of supraventricular tachycardia can be made with confidence, and ventricular tachycardia can be excluded with confidence.

3. In a case of rapid regular tachycardia, if there is wide splitting of both sounds, ventricular tachycardia is usually present.

4. In a case of rapid regular tachycardia, if there is wide splitting of both sounds, variation in the intensity of the first sound and independent, irregular "Cannon A" waves in the jugular venous pulse, the diagnosis of ventricular tachycardia can usually be made with confidence.

5. The wide splitting of both heart sounds is a manifestation of ventricular asynchrony; the variation in the intensity of the first sound and the independent, irregular "Cannon A" waves is a reflection of auriculoventricular dissociation.

6. Supraventricular tachycardia with bundle branch block, ventricular tachycardia with auricular fibrillation and ventricular tachycardia with retrograde conduction are all rare conditions, in which ventricular asynchrony occurs without auriculoventricular dissociation. Wide splitting of both heart sounds without variation in the intensity of the first sound is therefore encountered. Differentiation is difficult but can be made by careful study, as discussed.

7. The great value of the esophageal lead in the electrocardiographic diagnosis has been clearly demonstrated.

8. In a case of rapid regular tachycardia, if the electrocardiogram reveals a QRS interval of normal duration, the diagnosis of supraventricular tachycardia is established. Auricular activity can usually be demonstrated by standard electrocardiograms and esophageal leads are rarely necessary.

9. In a case of rapid regular tachycardia, if the electrocardiogram reveals a widened QRS, supraventricular tachycardia with bundle branch block cannot be differentiated from ventricular tachycardia, unless auricular activity is demonstrated. Whereas clinical evidence of auricular activity can be readily detected, the diagnosis cannot usually be made by the conventional electrocardiogram, as the P waves are often obscured by the widened QRS-T complexes. The esophageal leads, however, will clearly demonstrate P waves and thus overcome this problem.

10. The esophageal lead is essential in the differentiation of supraventricular tachycardia with bundle branch block, ventricular tachycardia with independent auricular activity, ventricular tachycardia with retrograde conduction, and ventricular tachycardia with auricular fibrillation.

11. The same clinical features that help to differentiate supraventricular tachycardia from ventricular tachycardia help to differentiate auricular from ventricular premature systoles.

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THE ELECTROCARDIOGRAM IN VENTRICULAR SEPTAL DEFECT: SCALAR AND VECTORIAL ANALYSIS OF THIRTY-TWO CASES

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THE electrocardiogram in ventricular septal defect has not yet been sufficiently studied. In general, it has been considered to be within normal limits.[1-4] Recently, it has been reported by Carlotti and associates[5] that the electrocardiographic modifications are similar to those encountered in atrial septal defect. This paper, which appears to be the most complete as far as the electrocardiographic study of ventricular septal defect is concerned, reached conclusions somewhat different from ours.

Since ventricular and atrial septal defects are malformations with different hemodynamic alterations, we believed that the electrocardiogram would also be different.

With this in mind we decided to undertake the present study.

MATERIAL AND METHOD

Thirty-two cases with the diagnosis of ventricular septal defect made by cardiac catheterization have been studied. Only in two subjects did the catheter pass from the right to the left ventricle; in the remaining cases, diagnosis was made by gasometric analysis.

In all cases the twelve usual leads were recorded by a Sanborn photographic apparatus. In an effort to investigate the course of the ventricular activation process, we undertook a special study with multiple and simultaneous thoracic leads in six cases using the Sanborn Polyviso four-channel electrocardiograph for direct simultaneous recording. The method has been used previously in our department and its detailed description appears elsewhere.[6]

The electrocardiograms were studied from the scalar and vectorial viewpoints.

Scalar Data.—The following scalar data were analyzed: P-Q and Q-T interval; duration, voltage, and morphology of the P wave, QRS duration; R wave voltage, R/R+S ratio (in those cases showing a polyphasic complex, we have considered the second positivity and the first negativity) and the intrinsicoid deflection time in V_1 and V_6.

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Vectorial Data.—In accordance with the method of Grant and Estes,[7] the mean spatial vectors of P, QRS, and T, the spatial angle between SÂQRS and SÂT and the main instantaneous vectors of the ventricular activation process[6] have been determined. For that purpose a plastic model, similar to that recently described by two of us,[6] was used. In this model the eccentricity of the apparent point of origin of the vectors and the elliptic form of the cylinder which represents the thorax are characteristic.* The spatial determinations of the mean vectors mentioned could not be performed accurately in cases in which the precordial leads did not show the isodiphasic transitional complexes. In these cases, however, it was possible to know whether the vector was oriented anteriorly or posteriorly.

For the electrocardiographic diagnosis of right ventricular hypertrophy† and right bundle branch block,‡ morphologic and vectorial criteria were followed.[8] Electrocardiographically, the diagnosis of left ventricular hypertrophy, incomplete left bundle branch block, combined hypertrophy of both ventricles, and auricular enlargment was sustained following the criteria supported by the Electrocardiographic Department of National Institute of Cardiology of Mexico.[9] The criteria followed in order to recognize ventricular septal hypertrophy will be discussed later.

The cases were divided into four groups according to the right ventricular systolic pressure.

Group 1: pressures up to 30 mm. Hg; five cases

Group 2: pressures between 31 and 60 mm. Hg; ten cases

Group 3: pressures between 61 and 80 mm. Hg; six cases

Group 4: pressures above 81 mm. Hg; eleven cases

In five cases the pressures recorded in the right ventricular cavity and in the pulmonary artery evidenced a pulmonary stenosis which was moderate in four cases and marked in one. In one instance an associated rheumatic mitral valve lesion was found.

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*The "electrical center" or origin of the electrical force for SÂQRS and SÂT is projected in V_2 and the "electrical center" for SÂP is about 2 cm. above V_1.

†According to the morphology in V_1, four types of right ventricular hypertrophy have been considered. In all of them, the QRS complex is predominantly positive due to the presence of an R wave of greater amplitude than normal. In the first, there is a small initial positivity which precedes the great and clean (without notching and slurring) R wave (rR). In the second, one observes an initial slurring of the ascending limb of R; in the third, the R wave is clean (R or Rs); and in the fourth the QRS complex shows a small early negativity, i.e., the QRS complex is of the qR type. These morphologic differences of the initial part of the QRS complex are merely a consequence of the projection of the septal vector[8] on V_1.

‡Three degrees of right bundle branch block have been considered. In the first, QRS duration is usually less than 0.10 second, and there is no slurring in the terminal part of QRS complex; the only sign suggestive of a conduction defect is a late second small positivity (r'). In the second, QRS duration is usually less than 0.12 second; in V_1 there is a late second positivity (r') of variable amplitude with a moderate slurring in its last part. In the third, QRS duration is generally greater than 0.12 second; in V_1 and sometimes in V_2 and V_3, a late positivity usually of important magnitude with terminal slurring is inscribed. Generally speaking, the first and second degree correspond to incomplete right bundle branch block, and the third degree, to complete right bundle branch block.

RESULTS

The results are summarized in the Tables I and II and in Figs. 1, 2, and 4.

Sex.—Of the thirty-two cases, twenty-two (68.75 per cent) were male and ten (31.25 per cent) female. It should be emphasized that there was an increase of males in the higher pressure groups with the result that in the fourth group there were ten men to only one woman.

TABLE I

GROUP	R.V.S.P.	AGE	SEX		V_1			V_6		
			M	F	R	R/R+S RATIO	I.D.T.	R	R/R+S	I.D.T.
1	29.70	15.40	2	3	4.53	0.37	0.025	13.50	0.82	0.038
2	50.90	11.60	6	4	14.60	0.48	0.045	22.65	0.81	0.040
3	68.00	8.16	4	2	23.46	0.91	0.049	15.36	0.59	0.038
4	101.27	14.45	10	1	19.38	0.80	0.051	33.77	0.70	0.050
Total group	67.15	12.21	22	10	17.57	0.68	0.046	20.79	0.78	0.043

The cases have been divided into four groups with regard to the systolic pressure values registered in the right ventricular cavity (see text). All figures represent average values except those in the column in which sex is analyzed. R and S values are given in tenths of a millivolt.

I.D.T. = Intrinsicoid deflection time

R.V.S.P. = Right ventricular systolic pressure

Age.—The average age in all groups was 12.21 years, varying between 3 years (one case of the second group and one of the third) and 29 years (a case of the fourth group). The average age in each group was 15.4, 11.6, 8.16, and 14.45 years, respectively (Table I).

P-Q Interval.—A first degree atrioventricular block was found in four cases (12.50 per cent of the total group). One of these cases was complicated by rheumatic heart disease, and the rheumatic activity was the probable cause of the atrioventricular block.

Q-T Interval.—Normal in all cases.

Auricular Complex (P wave); Scalar Data.—

Duration: According to age,[10] an increased duration of the P wave was found in twenty-three cases (72 per cent). The subject with rheumatic heart disease presented the maximum duration. It was normal in nine cases (28 per cent) and in six of these, it reached the maximum normal value for the age.

Voltage: It was increased in three cases in the limb leads: two cases showed the characteristics of "congenital P wave"[11] (one belonged to the second group and the other to the fourth) and one case was found to have a "mitral P wave" (the one with rheumatic heart disease). In V_1 the voltage of the P wave was increased in sixteen cases (normal value 0.16 mv.). The highest voltage in V_1 was 0.40 mv. (the case of the fourth group with a "congenital P wave").

Morphology and characteristics: In some cases, in spite of having a normal voltage, the P wave was peaked in the limb leads mainly in Lead II. In V_1 the P wave was positive in the majority of cases; in eight it was diphasic (+ −) and in the case with rheumatic heart disease the negative area was greater than the positive.

SÂP.—

Direction: ÂP varied from −30° to +85° (Fig. 1) with a mean value of +37.2°; however, in the majority of the cases it was found within the limits of +30° and +60°. If we exclude the only two cases with ÂP in Bailey's first sextant, the average is +44.53° which is quite similar to the ÂP average found in eighty normal subjects of less than 21 years of age (+44.75°).[12]

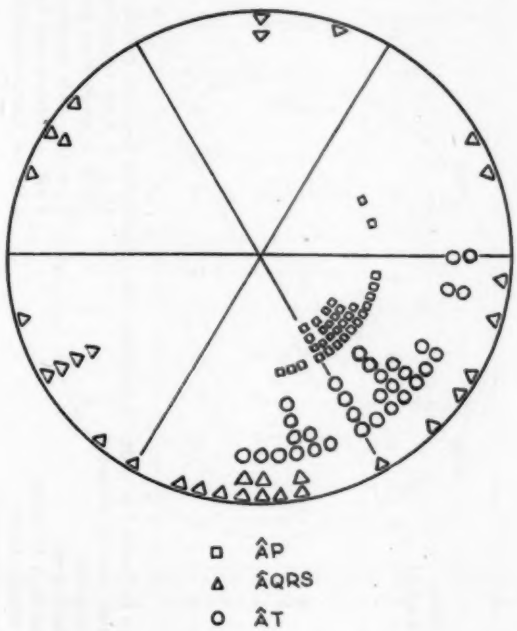


Fig. 1.—Frontal plane distribution of *ÂP*, *ÂQRS* and *ÂT*.

Only the case with rheumatic heart disease showed a backward projection of SÂP in the sagittal plane. In all of the remaining subjects, the vector had a forward or straight downward orientation. It is impossible to present an average of the spatial orientation of SÂP for, in the majority of the cases, we did not record multiple thoracic leads.

Magnitude: The greater voltage of the P wave in V_1 (one-half of the cases) indicates an increase in the magnitude of the vector since there was not a concomitant decrease in voltage in the limb leads.

We could not find a good correlation between the changes of the P wave and the right auricular mean pressure or the right ventricular systolic pressure. However, generally speaking, the subjects with normal pulmonary pressures had P waves with slight abnormalities.

TABLE II

GROUP	NO. CASES	R.V.S.P.	L.A.E.	R.A.E.	1ST D. A.V.B.	RBBB			RVH				LVH	CVH	LBBB	VSH	LDC
						I	II	III	I	II	III	IV					
1	5	29.7	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
2	10	50.9	4	2	2	1	0	2	1	2	1	0	7	5	1	2	2
3	6	68.0	3	0	1	0	1	0	3	2	0	0	4	4	0	2	3
4	11	101.27	4	1	1	0	0	0	1	4	5	1	9	9	0	4	5
Total group	32	67.15	11	3	4	1	2	2	5	8	6	1	20	18	2	8	10

The pressure-column is the same as that shown in Table I in order to facilitate the relationship between pressure values and electrocardiographic findings.

RVSP = Right ventricular systolic pressure
LAE = Left atrial enlargement
RAE = Right atrial enlargement
1st D A.V.B. = First degree A-V block
RBBB = Right bundle branch block
RVH = Right ventricular hypertrophy
LVH = Left ventricular hypertrophy
CVH = Combined ventricular hypertrophy
LBBB = Left bundle branch block
VSH = Ventricular septal hypertrophy
LDC = Large diphasic complex

In summary, there is a longer duration of the auricular activity and the SÂP magnitude increases slightly. There were no important modifications in the spatial direction of this vector. Definite signs of left auricular enlargement were noted in eleven cases, and of right auricular enlargement in three.

Ventricular Complex (QRS).—

Duration: The mean duration of the QRS complex was 0.092 sec., and no significant group differences were found.

R wave in V_1: The mean voltage of the R wave in V_1 was 17.57 mm. with a range from 3.16 to 34 mm. In each group the average was 4.53, 14.60, 23.46, and 19.38 mm., respectively.

R/R+S ratio: The average for all the groups was 0.68 mm. In each group the average was 0.37, 0.48, 0.91, and 0.80 mm., respectively.

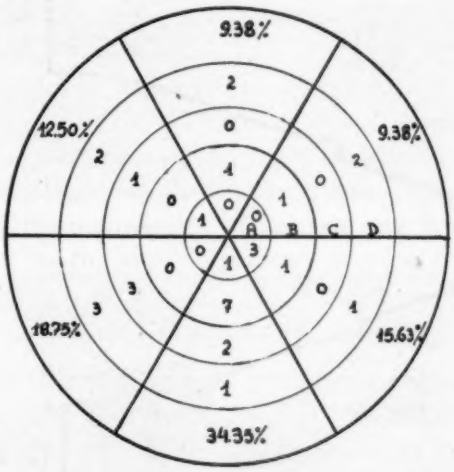


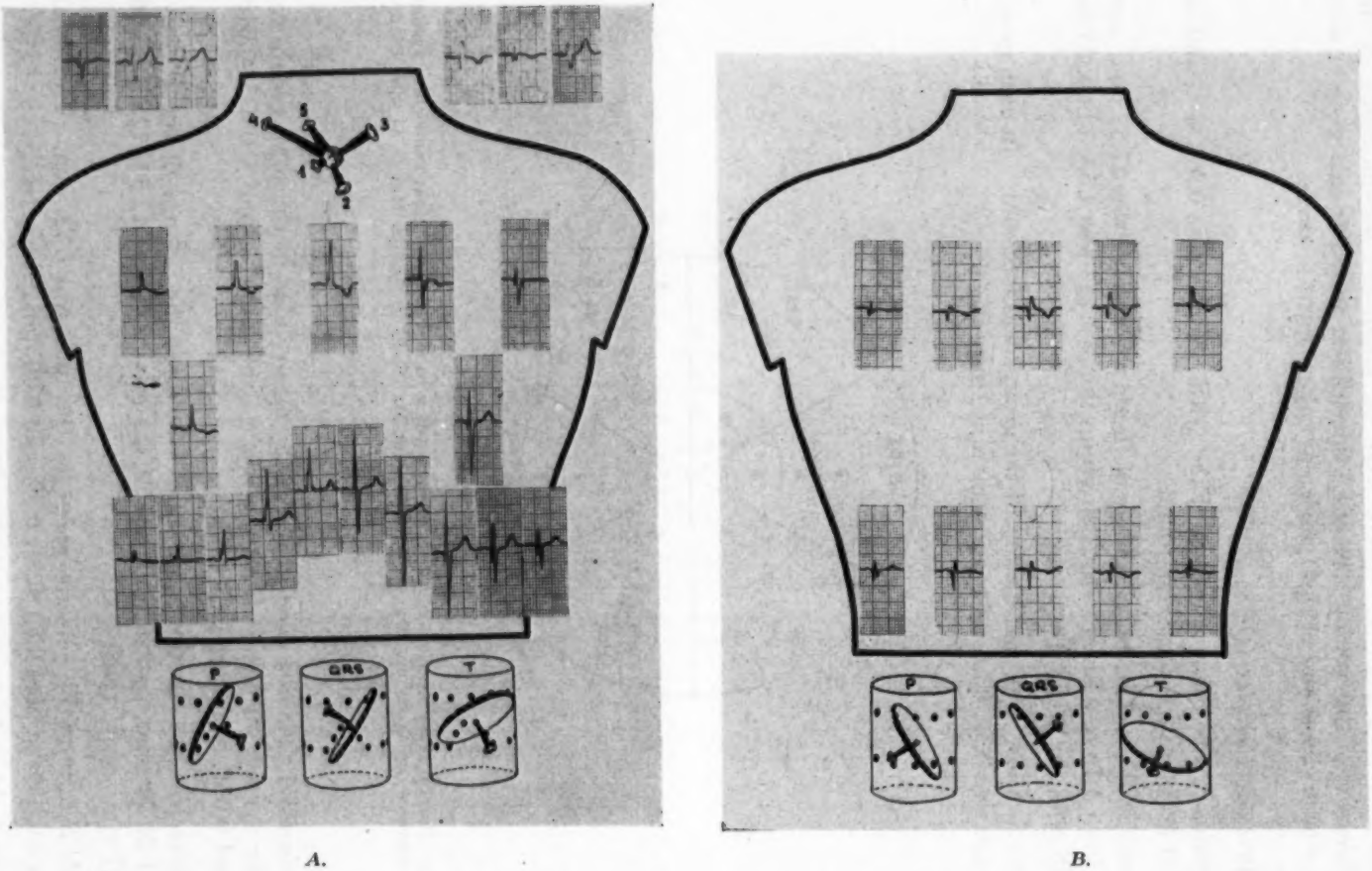
Fig. 2.—Frontal plane distribution of ÂQRS according to the degree of right ventricular systolic pressure. Circle *A*, up to 30 mm. Hg; *B*, 31 to 60 mm. Hg; *C*, 61 to 80 mm. Hg; *D*, 81 mm. Hg and up.

Intrinsicoid deflection time in V_1: The mean value in the total group was 0.046; the average increased from the first to the fourth group: 0.025, 0.045, 0.049, and 0.051, respectively.

R Wave in V_6: In the total number of cases the voltage of the R wave averaged 20.79 mm., and in each one of the groups it was 13.50, 22.65, 15.36, and 33.77 mm., respectively.

R/R+S ratio in V_6: The average for the total was 0.78 mm. The mean value for each group was 0.82, 0.81, 0.59, and 0.70 mm., respectively.

Intrinsicoid deflection time in V_6: The average for the total number of cases was 0.043 second and in each group: 0.038, 0.040, 0.038 and 0.050 second, respectively (Table I).



A. *B.*

Fig. 3—*A*, Anterior thoracic map of a case corresponding to the fourth group. The spatial orientation of five instantaneous vectors of the ventricular activation process is shown at the top of the figure. $S\bar{A}P$, $S\bar{A}QRS$ and $S\bar{A}T$ are represented at the bottom of the figure. *B*,—Posterior thoracic map of the same case as *A*.

The Q wave in V_6: In several cases a deep Q wave was found in V_6. The mean voltage for the total was 4.1 mm., and the extreme limits were 0 and 18 mm. (a case of the fourth group). The depth of the Q wave increases progressively from the first to the fourth group: the averages were 2.0, 3.14, 4.84, and 6.44 mm., respectively. Several of the cases with a deep Q wave in V_6 showed an initial positive deflection or an initial slurring in V_1 which was inscribed simultaneously with the apex of the Q wave in the left precordial leads.

Large ventricular diphasic complexes: These were recorded mainly in V_2, V_3, and V_4 and were generally associated with a deep Q wave in V_5. This type of complex was found in ten (31 per cent of the total number of cases, two in the second, three in the third, and five in the fourth group).

SÂQRS.—

Direction: The ÂQRS may take any direction in the frontal plane (Fig. 1) although it was predominantly found in the fifth and fourth sextants. In Fig. 2 the distribution of ÂQRS in each sextant is correlated with the four groups of right ventricular systolic pressure.

Magnitude: With the exception of the first group, an increase in the magnitude of SÂQRS was found in the majority of the patients. This was found to be true since an increased voltage of QRS was recorded in the frontal and horizontal plane as well as in the multiple thoracic leads.

In summary, SÂQRS increases in magnitude and is deviated upward, forward, and to the right as the systolic pressure increases in the right ventricle.

INSTANTANEOUS MEAN VECTORS

In six cases several instantaneous vectors of the ventricular activation process were studied. The first vector, which has been referred to as due to septal activation[6], is inscribed, as in normal cases, between 0.008 second and 0.013 second after the beginning of the ventricular complex. This vector is oriented forward and to the right in all cases. Downward deviation was found in almost all subjects. This orientation differs from that frequently observed in right ventricular hypertrophy.[13] The magnitude of this "septal vector" is greater than that found in normal subjects and in cases with right ventricular hypertrophy. Following the first vector, we took into consideration other instantaneous vectors which are inscribed up to 0.045 second after ventricular depolarization had begun. These vectors belong to the left ventricle and are easily determined by means of thoracic mapping, without the recording of a vectorcardiogram. They show an increased magnitude and are oriented forward, downward, and to the left. These characteristics are not seen in normal cases[6] or in ventricular hypertrophy.[13] After those electrical forces of the left ventricle, other vectors of important magnitude were determined. Their orientation was backward, to the right, and generally, upward. This peculiar sequence of ventricular activation is characteristic of ventricular septal defect. This is probably due to the combined hypertrophy of the free walls as well as the interventricular septum (Fig. 3, *A* and *B*).

THE T WAVE

In seven cases with signs of left ventricular hypertrophy, the T wave had the characteristics described in diastolic overloading of the left ventricle.[10]

SÂT

The frontal projection of SÂT was found between 0° and +95° (Fig. 1). The average location was +52.3, i.e., it was slightly deviated to the right. In one-third of the cases in which ÂT was located in the fifth sextant, the ÂQRS frequently presented an upward projection.

In most of the cases, the projection of SÂT on the sagittal plane was forward or straight downward. In only two cases did SÂT have a backward direction. It is important to emphasize that SÂQRS and SÂT presented a forward direction.

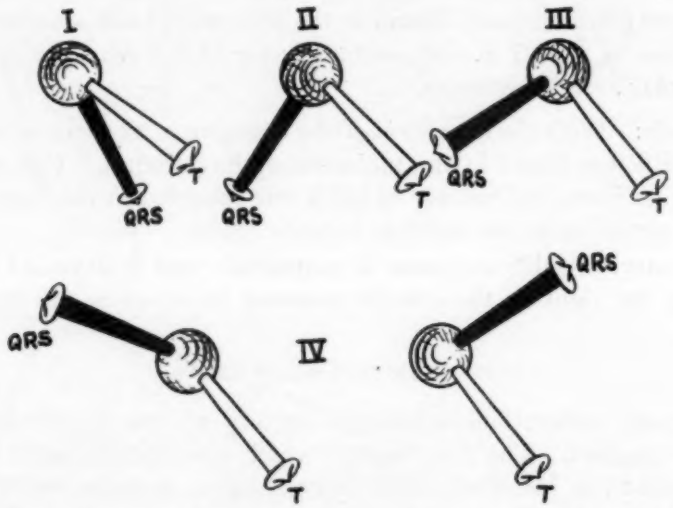


Fig. 4.—SÂQRS and SÂT orientation in each group according to the pressure values in the right ventricle.

Contrary to what is usually found in normal subjects under 15 years of age, the SÂT is directed forward. In spite of this, there are no important differences in the distribution of positivity and negativity of T on the body surface,[6] since in both cases the SÂT is directed downward and to the left. Nevertheless, the forward orientation of this vector explains the positive T waves commonly found in precordial leads, including V_1. This is infrequently seen in normal young subjects.[12] In three cases (Fig. 5) there was an isolated region of negativity within the positive T area at the level of V_3 and V_4. In these cases the heart beat was forceful. This correlation had been previously noted by Grant and Estes.[7]

The spatial angle between SÂQRS and SÂT increases from the first to the fourth group. The values were normal in the first two groups and definitely abnormal in the last two. The increased angle was fundamentally due to the shifting of SÂQRS (Fig. 4).

As the systolic pressure increases in the right ventricle, SÂQRS is deviated to the right, upward, and forward; SÂT tends to rotate slightly to the right and the SÂQRS-SÂT angle increases (Fig. 4). It is interesting to note that SÂQRS had a forward orientation even in the cases in which it was directed upward and to the left (Fig. 4). This particular orientation is not observed in normal cases or in left ventricular hypertrophy.

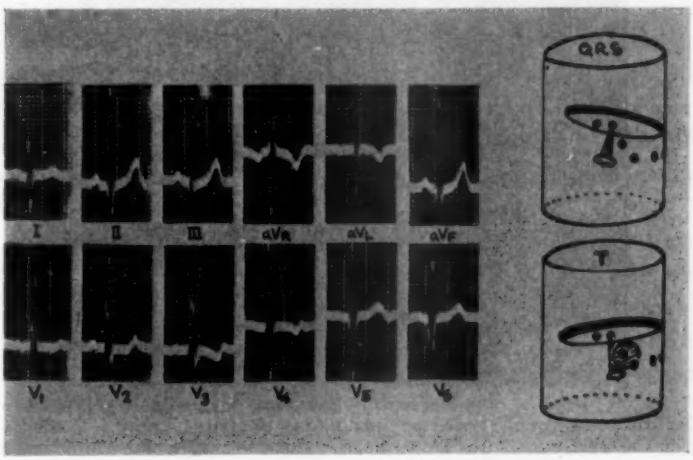


Fig. 5.—Electrocardiographic tracing and spatial orientation of QRS and T of a case from the third group. Notice in the inferior cylinder an isolated area of negativity (over V_2 and V_3) within the positive electrical field of SÂT. Electrocardiographic diagnosis of septal and combined ventricular hypertrophy was made.

VENTRICULAR HYPERTROPHY AND BUNDLE BRANCH BLOCK

Left ventricular hypertrophy was found in twenty cases. It was absent in Group 1, present in all cases of Group 4, except two which had an associated pulmonary stenosis. It was found less frequently in Groups 2 and 3. Signs of left ventricular diastolic overloading were observed in seven cases, five of which belonged to Group 2. First degree incomplete left bundle branch block was observed in one case in each of the first and second groups. There was right ventricular hypertrophy in twenty cases. It was found in every case in Group 4, and it was not present in Group 1 (see Table II). Five cases showed complete or incomplete right bundle branch block without signs of right ventricular hypertrophy. Four of these cases belonged to the first two groups. Combined ventricular hypertrophy was found in eighteen cases, and its incidence in the four groups increased parallel with the degree of right ventricular systolic pressure. Signs of septal hypertrophy (see Discussion) were found in eight cases, four of which were in the last group.

DISCUSSION

In ventricular septal defect there is a great predominance of males (68.8 per cent) contrary to what has been found in cases of patent ductus arteriosus (18 per cent)[14] and in atrial septal defect (20 per cent).[15]

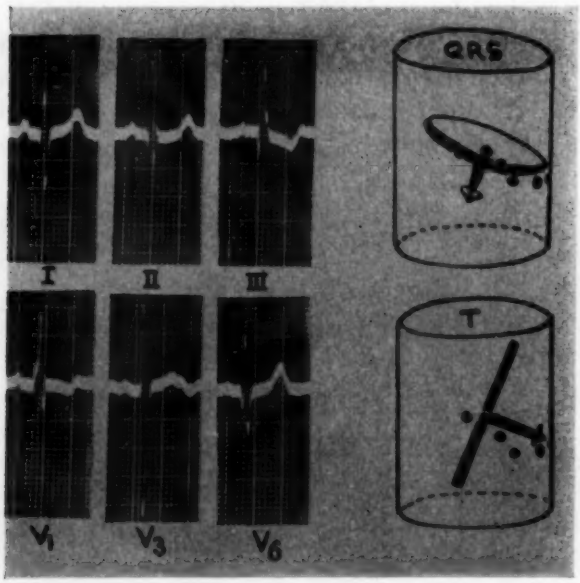


Fig. 6.—Electrocardiogram of a case corresponding to the fourth group. V_1 shows a QRS complex with a slurring on the upstroke of R. In V_3 a large diphasic ventricular complex is observed. Diagnosis of combined ventricular hypertrophy was made.

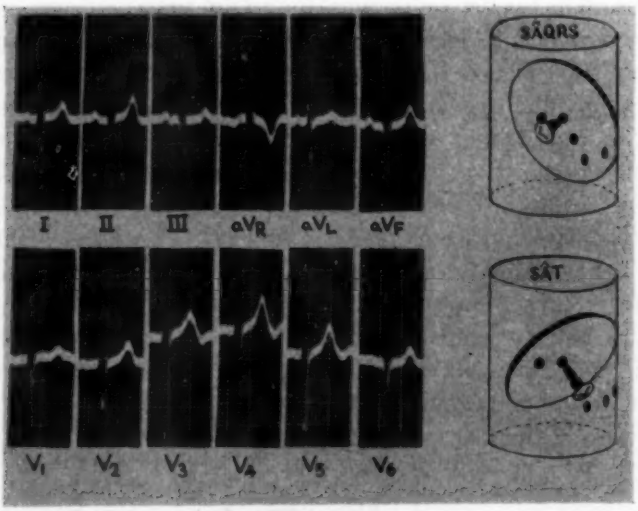


Fig. 7.—Electrocardiogram corresponding to the second group. V_1 shows a QRS complex of Rs type and the ascending part of R is clean. In V_3 and V_4 a large diphasic ventricular complex is observed. Diagnosis of combined ventricular hypertrophy was made.

Only four cases were over 20 years of age. A clear relation between age and the degree of pulmonary pressure was not observed as in cases of patent ductus arteriosus.[14]

It has been pointed out that ventricular septal defect does not show important electrocardiographic modifications.[1-4] Normal electrocardiograms, however, have been found in only three cases, and they belonged to the first group with normal pulmonary pressure. Probably in these cases there are small septal defects with unimportant left-to-right shunts. In the remaining twenty-nine cases the electrocardiogram was abnormal. In almost one-half of the tracings there were signs of atrial enlargement, mainly of the left auricle. This was probably due to the increased volume of blood handled by this cavity. It has been pointed out[5] that a first degree atrioventricular block is a common finding in this disease. In our tracings this was not found to be the case.

The most remarkable electrocardiographic modifications pertain to the ventricular complex. Combined ventricular hypertrophy is a very frequent finding. Hypertrophy of the left as well as of the right ventricle was observed more often as the pressure in the lesser circulation increased. It is important to point out that although the pulmonary pressure may be exceedingly high, the systemic pressure is always greater. We believe that due to the existence of this pressure gradient in favor of the left ventricle the electrocardiographic evidence of left ventricular hypertrophy is not masked by a marked right ventricular hypertrophy, as is observed in patent ductus arteriosus with reversed shunt. For this reason the left ventricular hypertrophy is greater as the pulmonary pressure increases.

Diastolic overloading of the left ventricle[10] is frequent in the second group and rare in Groups 3 and 4, which is probably due to a decrease in the volume of the shunt. Similar findings have been seen in cases of patent ductus arteriosus.[10]

The morphology of the QRS complex in V_1 in cases with right ventricular hypertrophy is similar to that found in congenital heart disease with predominant systolic overloading of the right ventricle.[13] Usually, this complex is predominantly positive, has a high voltage, and occasionally reaches a maximum duration of 0.12 second. In some cases there is an initial positivity (Fig. 5), in others an initial slurring (Fig. 6), while in others the ascending part of the R wave is clean (Fig. 7), and in only one case was there a small initial negativity (Fig. 8). These differences in morphology of the initial part of the QRS complex depend on the projection of the "septal vector" on Lead V_1. Some tracings especially in Group 4 show an initial positivity of increased voltage in V_1 and a deep Q wave in V_6 (Fig. 5). The vectorial analysis demonstrated that both deflections correspond to a large "septal vector" with a normal inscription time. We believe that this is due to hypertrophy of the interventricular septum. In favor of this hypothesis we have recorded increased R waves in the right ventricular cavity in some of our cases. In one case which showed a Q wave in all precordial leads, the right intraventricular tracing was of the qrS type and the septal vector was downward, to the right, and backward (Fig. 8). Thus it seems that in such a case the septal activation would be reversed because of a right septal mass predominance. These findings make it desirable to carry out

post-mortem studies in order to prove or disprove the existence of septal hypertrophy. Right or left bundle branch block without signs of ventricular hypertrophy is rarely found and when it exists it is almost always in the first two groups.

The vectorial study of the electrocardiogram in ventricular septal defect is characteristic. The SÂT vector orientation is similar to that observed in pulmonary stenosis, that is, downward, to the left, and forward. Contrary to that observed in other congenital heart disease, the SÂQRS is found in all sextants of the frontal plane. In Group 4 the upward and forward orientation was predominant.

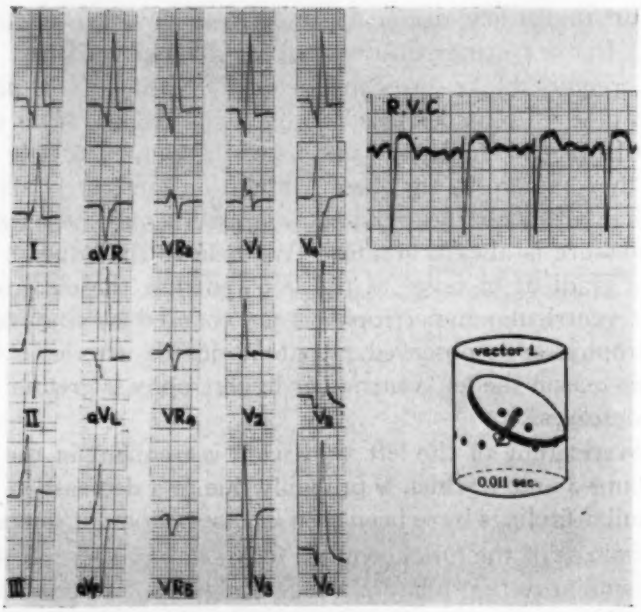


Fig. 8.—Limb and thoracic leads recorded simultaneously with aV_L as a control lead (upper row) in a case from the fourth group. A tracing recorded in the right ventricular cavity is also presented (*R.V.C.*). Notice the presence of a Q wave from V_1 to V_6 and QS and qrS complexes in the intracavitary record. The spatial orientation of Vector 1 (septal vector) is represented in the cylinder.

The most important electrocardiographic sign in ventricular septal defect is the presence of combined ventricular hypertrophy. This is not observed in atrial septal defect. We believe that the electrocardiogram of patent ductus arteriosus with moderate pulmonary hypertension is very similar to that seen in ventricular septal defect. There are, however, some electrocardiographic differences. The upward ÂQRS, the polyphasic QRS in V_1, and the large ventricular diphasic complexes are observed frequently in ventricular septal defect while they are exceptional in patent ductus arteriosus. There are also differences in the morphology of QRS complex in the left precordial leads. In both cases there is an R wave of increased voltage which follows a deep Q wave, but in the ventricular septal defect there is a deep S wave which is rare in patent ductus arteriosus.

In summary, the electrocardiographic signs of ventricular septal defect are:

1. Right ventricular hypertrophy with systolic overloading of the right ventricle: (a) tall R wave in V_1 and V_2; (b) QRS complex of the rR, Rs, R, and qR type.

2. Left ventricular hypertrophy with or without diastolic overloading of the left ventricle in V_5 and V_6: (a) tall or normal R wave when a small deflection was expected due to the accentuated right ventricular hypertrophy; (b) deep Q wave; (c) delayed intrinsicoid deflection; (d) positive T wave; (e) frequent complexes of qRs type with a positive T wave.

3. Suggestive data of septal hypertrophy: deep Q wave in V_5 and V_6 which is inscribed simultaneously with the first positivity of a complex of the rR type in V_1.

4. Large diphasic complexes in V_2, V_3, V_4 and on occasion in the limb leads.

SUMMARY

The electrocardiographic characteristics of thirty-two cases of ventricular septal defect have been analyzed. In the majority of cases the electrocardiographic pattern is diagnostic or strongly suggests this congenital defect.

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THE IMPORTANCE OF ELECTROCARDIOGRAPHIC PATTERNS IN CONGENITAL HEART DISEASE

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RECENT textbooks on electrocardiography do not sufficiently discuss the electrocardiographic patterns of congenital heart disease, and the majority consider the electrocardiogram as of minor diagnostic importance. Recent research performed in the Electrocardiographic Department of the Instituto Nacional de Cardiología de México has clearly shown that the electrocardiographic study is a valuable element in the diagnosis of congenital heart disease. There are many tracings which disclose the hemodynamic alterations more accurately than the clinical and radiologic findings.

GENERALITIES

The electrocardiographic modifications encountered in these diseases depend, among other factors, on myocardial changes, hypertrophy of the free ventricular walls, and/or the intraventricular septum, dilatation of cardiac cavities, and the position of the heart. All of these are most probably a consequence of the primary hemodynamic disturbances.

Cabrera and associates[1-3] were the first to establish the relationship between hemodynamic and electrocardiographic alterations. The authors present electrocardiographic evidence of differences in behavior of the heart, according to the type of hemodynamic overloading. They differentiate two types of overloading for each ventricle: systolic and diastolic. The systolic overloading of the right ventricle gives rise to high R waves and negative symmetrical T waves in right precordial leads. The diastolic overloading of the right ventricle is manifested by incomplete or complete right bundle branch block. The systolic overloading of the left ventricle produces flat or negative T waves as well as a negative displacement of the RS-T segment in the left precordial leads. The diastolic overloading of the left ventricle produces high symmetrical T waves, increased R waves, and delayed intrinsicoid deflection in the left precordial leads. Of course, these electrical alterations may depend on many different factors; however, the importance of the hemodynamic changes may be seen in tracings obtained before and after surgical intervention in such diseases as patent ductus arteriosus, atrial septal defect, and mitral stenosis. For example, the left ventricular diastolic overloading of patent ductus arteriosus is replaced by a transitory systolic overloading of the same ventricle after operation.

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In addition to the usual electrocardiographic descriptions, it is of great importance to attempt to infer hemodynamic disturbances in tracings of congenital heart disease. If this can be done, we will be able to approach the diagnosis, prognosis, and treatment in a physiologic manner.

Electrocardiographic criteria used in our department to recognize some of the congenital heart diseases will be pointed out. Some congenital conditions will not be described because of the lack of electrocardiographic evidence necessary for their identification.

ELECTROCARDIOGRAPHIC PATTERNS IN ACYANOTIC CONGENITAL HEART DISEASE

1. *Atrial Septal Defect (ASD).*—Vizcaino and associates[4] were among the first to point out the great incidence of right bundle branch block (RBBB) in this disease. Limón and associates[5] recently published a detailed study of fifty cases. A summary of their findings follows:

Auricular complex: The P wave was normal in 32 per cent of the cases. Slight changes were found such as increased duration and notching in 30 per cent of the cases. It was definitely abnormal in the rest. When there were peaked P waves with increased duration (0.12 second or more) and greater voltage, enlargement of both atria was suggested. The morphology was a combination of "mitral P" plus "congenital P".

Atrioventricular conduction defect: First degree atrioventricular block was found in 26 per cent of the cases.

Ventricular complex: Incomplete RBBB (80 per cent) or complete RBBB (6 per cent) are the most frequent findings (Fig. 1). Only in a few cases (8 per cent) did the QRS complex show characteristics of right systolic overloading with right ventricular hypertrophy (high R waves in V_1 and V_2) (Fig. 2). High pulmonary hypertension and venous-arterial shunt were present in these cases. T-wave modifications are not characteristic and appear secondary to the bundle branch block or to the right ventricular hypertrophy.

The ÂQRS varied from $+90°$ to $+170°$. Only in one case was ÂQRS located at $-110°$. It is interesting to point out that, generally, ÂQRS shifts more to the right as pulmonary hypertension increases.

According to Cabrera and Monroy[1,2] the RBBB could be the electrocardiographic manifestation of the right ventricular diastolic overloading produced by the arteriovenous shunt. Atrial septal defect is seldom followed by moderate or marked pulmonary hypertension which explains the scarcity of electrocardiographic signs of right systolic overloading with right ventricular hypertrophy.

Only once was the electrocardiogram normal. In this case the catheter passed through the septal defect which established the diagnosis. Gasometric analysis gave no clue as to the existence of this defect.

2. *Ventricular Septal Defect.*—It is common knowledge that ventricular septal defect does not show important electrocardiographic changes. Recently, Carlotti and associates[8] asserted that ventricular and atrial septal defects are

similar as far as the electrocardiogram is concerned. However, if we take into account the fact that the hemodynamic changes in both diseases are not similar, we should also expect electrocardiographic differences.

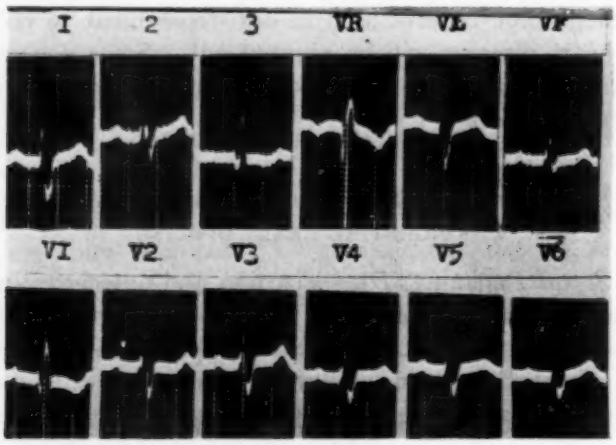

Fig. 1.—Right bundle branch block in a case of atrial septal defect.

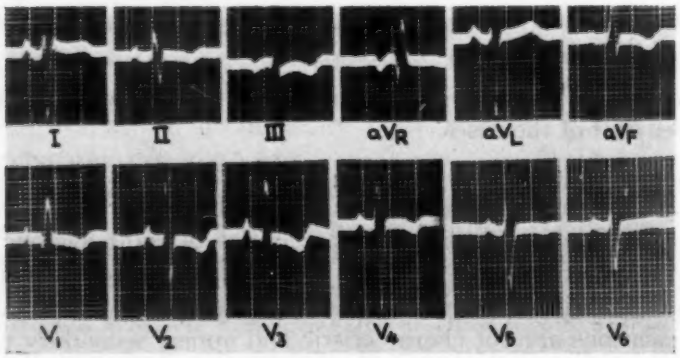

Fig. 2.—Right bundle branch block in a case of atrial septal defect with marked pulmonary hypertension. In V_1 the ventricular complex is of the qR type.

In our department Marsico and associates[9] have lately reviewed thirty-two cases of this congenital heart disease. Their most important findings can be summarized as follows:

Auricular complex: In 70 per cent of the cases the P-wave duration was increased. Left auricular enlargement was found in 30 per cent and right auricular enlargement in 10 per cent.

Atrioventricular conduction defect: First degree atrioventricular block was noted in 12 per cent of the cases.

Ventricular complex: Right ventricular hypertrophy of the systolic overloading type was observed in 62 per cent of the cases. This kind of hypertrophy is manifested in the electrocardiographic tracings by a QRS complex which is

predominantly positive in V_1 and V_2. The most common types are: rR, Rs, qR, R, with or without initial slurring on the upstroke of the greatest R (Fig. 3). The electrocardiographic signs of right ventricular hypertrophy with systolic overloading are the same as those found in ventricular septal defect as well as in any other congenital or acquired heart disease complicated by systolic hypertension of the right ventricle. (Some cases of mitral stenosis as well as chronic cor pulmonale may also give this picture.) Generally, the T wave is positive in the right precordial leads.

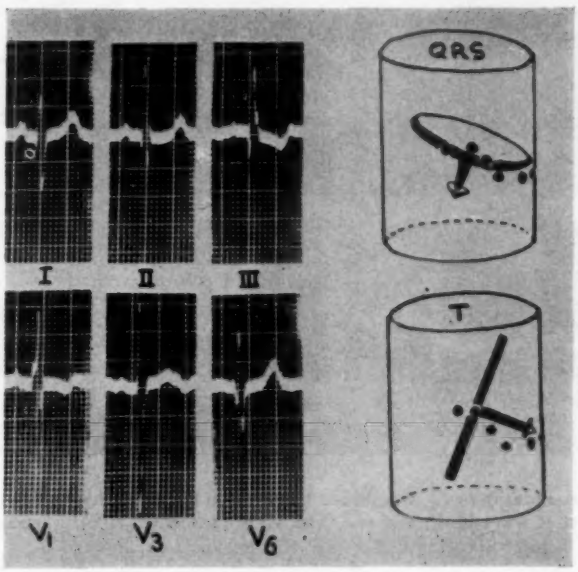

Fig. 3.—Ventricular septal defect. The tracings suggest combined ventricular hypertrophy. The deep Q wave in V_6 and the large diphasic complex of V_3 are very common signs of this anomaly.

In the majority of the cases there were signs of left ventricular hypertrophy (62 per cent). In those cases in which the systolic pressure of the right ventricle does not exceed 60 mm. Hg, the hypertrophy seems to be caused by diastolic overloading of the left ventricle. The QRS complex in V_5 and V_6 was similar to that observed in the same leads in cases of patent ductus arteriosus, but contrary to that which is found in this disease: the R wave in V_5 and V_6 is frequently followed by a deep S wave. When the right ventricular systolic pressure was higher than 60 mm. Hg, the electrocardiogram did not show left ventricular diastolic overloading. Combined hypertrophy of both ventricles was found in 56 per cent of all cases.

Marsico and associates[9] speak of hypertrophy of the interventricular septum when, in the presence of combined ventricular enlargement, there is an abnormally deep Q wave in V_6 which is inscribed simultaneously with the first positivity (generally of increased magnitude) of an rR complex in the right precordial leads (Fig. 4). Large diphasic complexes (sign of Katz and Watchell) were

recorded in V_2, V_3, and V_4, and sometimes in the limb leads (31 per cent of the cases). It should be emphasized that ventricular hypertrophy in the free wall as well as in the interventricular septum increases in a direct relation to the degree of right ventricular systolic pressure.

Incomplete or complete bundle branch block without any evidence of ventricular hypertrophy was observed in 22 per cent of the tracings and in these cases the right systolic pressure was moderately increased.

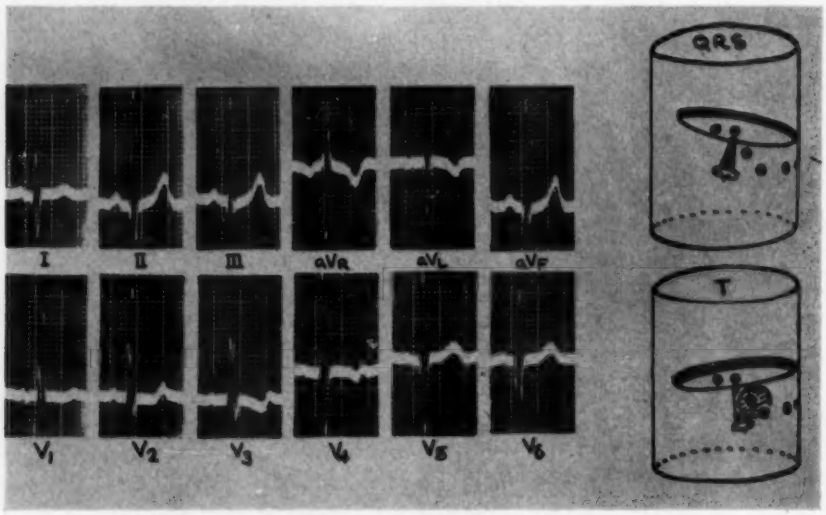

Fig. 4.—Ventricular septal defect. Combined ventricular hypertrophy with a deep Q wave in V_6. The first R wave in V_1 and the Q of V_6 are inscribed simultaneously.

ÂQRS was found in all sextants of the frontal plane, but its direction was upward and to the right when marked pulmonary hypertrophy was present. In three cases of ventricular septal defect, ÂQRS was deviated to the left (Fig. 5).

Only in cases with normal pulmonary pressure was a normal electrocardiogram observed. Pulmonary hypertension is frequently found in ventricular septal defect. This is evidenced by the fact that only five cases of our series had a normal pulmonary pressure. The high diagnostic value of the electrocardiogram can be explained by these hemodynamic changes.

In summary, the electrocardiographic signs of ventricular septal defect are:

Right ventricular hypertrophy with systolic overloading of the right ventricle: (a) tall R wave in V_1 and V_2; (b) QRS complex of the rR, Rs, R, and qR type.

Left ventricular hypertrophy with or without diastolic overloading of the left ventricle, in V_5 and V_6: (a) tall or normal R wave when a small deflection was expected due to the accentuated right ventricular hypertrophy; (b) deep Q wave; (c) delayed intrinsicoid deflection; (d) positive T wave; (e) frequent complexes of qRs or qRS type with a positive T wave.

Suggestive data of septal hypertrophy: deep Q wave in V_5 and V_6 which is inscribed simultaneously with the first positivity of a complex of the rR type in V_1.

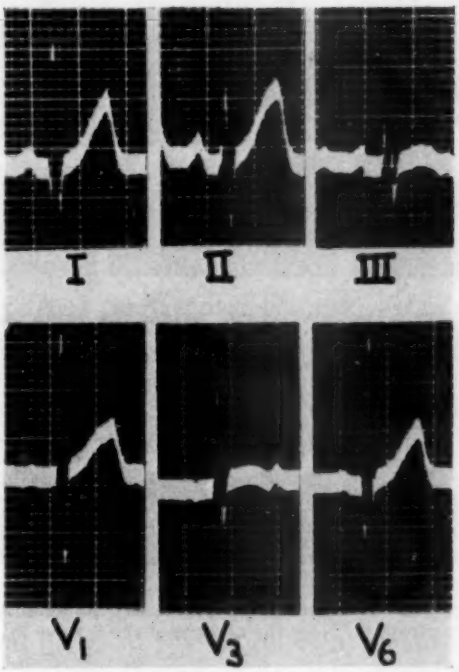

Fig. 5.—Ventricular septal defect. Combined ventricular hypertrophy with a deep Q wave in V_6. The ĀQRS is deviated to the left.

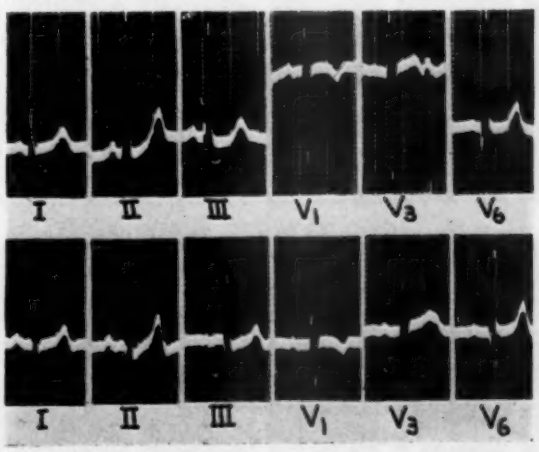

Fig. 6.—Two cases of patent ductus arteriosus without pulmonary hypertension. Left ventricular hypertrophy with diastolic overloading of the left ventrical. The T wave in V_6 is peaked and tall (precordial leads were taken with 1 millivolt = 0.5 cm.). There is a delay in the inscription of the intrinsicoid deflection.

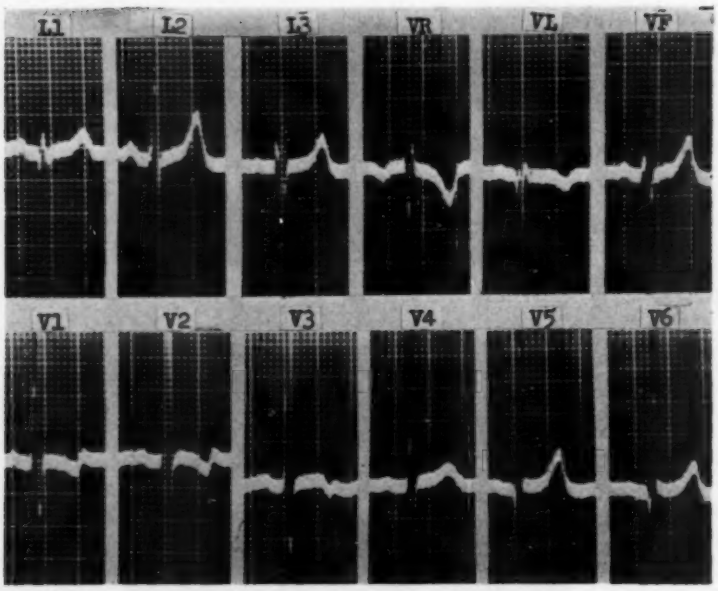

Fig. 7.—Patent ductus arteriosus with moderate pulmonary hypertension. Combined ventricular hypertrophy. Note the absence of the S wave in V_6.

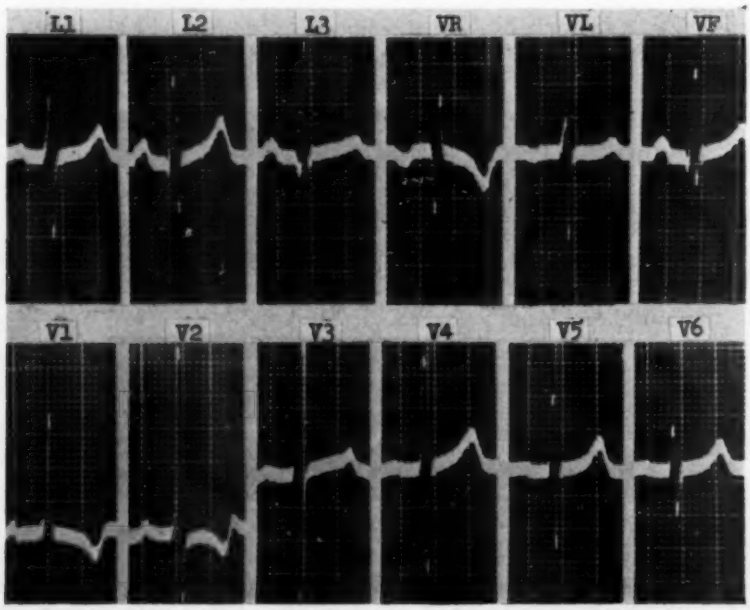

Fig. 8.—Patent ductus arteriosus with marked pulmonary hypertension. The tracing shows right ventricular hypertrophy. The signs of left ventricular hypertrophy are masked.

Large diphasic complexes in V_2, V_3, and V_4 and on occasion in the limb leads.

3. *Patent Ductus Arteriosus (PDA).*—It has been stated that in this disease the electrocardiogram has no diagnostic value. Cabrera and associates[3] were first to describe a characteristic electrocardiographic pattern in these cases.

Fundamentally, three degrees can be differentiated: (a) PDA without pulmonary hypertension; (b) PDA with moderate pulmonary hypertension; (c) PDA with high pulmonary hypertension.

Left ventricular diastolic overloading is shown in PDA without pulmonary hypertension. High peaked symmetrical T waves are seen in the left precordial leads together with signs of left ventricular hypertrophy. In these cases the QRS complex in V_1 is normal (Fig. 6).

In cases with moderate hypertension, electrocardiographic evidence of right ventricular systolic overloading with right ventricular hypertrophy are observed in V_1. These signs are added to those of left ventricular overloading; in other words, there is combined ventricular hypertrophy (Fig. 7). Such a pattern is similar to that of ventricular septal defect, but there are some characteristics which help in establishing the differential diagnosis. The positive complexes in V_1, the large diphasic complexes in V_2, V_3, and V_4, persistent S wave in V_5 and V_6, and the great shift to the right or upward of $\hat{A}QRS$ are valuable signs in favor of ventricular septal defect and are rarely found in PDA.

When the pulmonary hypertension reaches values similar to those of the systemic circulation and even higher, there is an increase in the signs of right ventricular systolic overloading with right ventricular hypertrophy. At the same time the signs of left ventricular hypertrophy are masked (Fig. 8).

The P wave may be of increased duration, and in some tracings there are signs of left atrial hypertrophy.

The average direction of $\hat{A}QRS$ is located around $+45°$ in those cases with a pulmonary pressure around 40 mm. Hg, to $+68°$ when the pulmonary pressure reached 80 mm. Hg, and around $+100°$ when the pressure was above 80 mm. Hg. Thus, the $\hat{A}QRS$ vector is deviated more and more to the right as the pressure in the pulmonary circuit increases, but it does not reach the superior sextants of the frontal plane.

The electrocardiographic pattern of PDA changes immediately after surgical intervention. A few days after the ligation of the ductus the T-wave voltage decreases or becomes negative. In some cases, the RS-T segment shows negative displacement similar to that seen in arterial hypertension. These changes are due to the transitory systolic overloading of the left ventricle.[3]

Once more, in this congenital defect, a close correlation between hemodynamic and electrocardiographic changes is observed.

Recently, we have had the opportunity to see some tracings of incomplete left bundle branch block with a positive and peaked T wave in the left precordial leads, when a flattened or negative T due to the concomitant bundle branch block would have been expected. In a very few cases there is a complete or incomplete right bundle branch block.

4. *Electrocardiographic Patterns in Cyanotic Congenital Heart Disease.*—Zuckermann and collaborators[6,7] described in Lead I and Lead II a tall peaked, widened and notched P wave in some congenital heart conditions with cyanosis. These were principally found in the tetralogy of Fallot, tricuspid atresia, and transposition of the large vessels. The ÂP axis was situated bteween +40 and +60°. In some cases this type of P was seen in Lead II and Lead III instead of in Lead I and Lead II. In V_1 and V_2 the P wave was peaked and predominantly positive. The P wave with these characteristics has been referred to by these authors as the "congenital P" which mainly depends on two fundamental factors: (1) dilatation or hypertrophy of the right atrium (post-mortem studies have shown that the capacity of the right atrium is three times greater than that of the left); and (2) the horizontal position of the heart.

In other conditions there are similar P waves; these are chronic cor pulmonale, during the first stages of general anesthesia, in dogs subjected to hypoxia and in human beings with a decrease in blood oxygen saturation.

Recently, Peñaloza and collaborators,[10] on studying pure or complicated pulmonary stenosis, found that the "congenital P" was present very often in cases with a lowered oxygen saturation of the arterial blood. The change occurred when the O_2 saturation reached 71 per cent. Generally speaking, there is an inverse relationship between the degree of saturation and the changes in the P. Nevertheless, the "congenital P" was also found, but less frequently, when there was an elevation of the right ventricular systolic pressure usually above 130 mm. Hg. The cases with a low-oxygen saturation and a high systolic pressure in the right ventricle are those which produce the most striking P-wave changes.

In conclusion, we must accept that there are various factors which determine the P-wave changes seen in these cardiopathies: dilatation or hypertrophy of the right atrium, position of the heart, low-oxygen saturation in the arterial blood, and a systolic overloading of the right ventricle.

Even though there is no cyanosis in pure pulmonary stenosis we have included this disease in the cyanotic group because from the electrocardiographic point of view the situation is the same whether or not pulmonary stenosis is pure or complicated. This group of congenital cardiopathies has been studied in our department by Zuckermann and collaborators[6,7] and a short while ago the subject was reviewed by Peñaloza and his colleagues.[10] We will summarize the principal findings.

Pure Pulmonary Stenosis.—The electrocardiogram of pure pulmonary stenosis may vary from normal or slight alterations to tracings representing maximum right ventricular hypertrophy of the systolic overloading type. These wide variations depend on the systolic hypertension of the right ventricle and on the degree of pulmonary stenosis and right ventricular hypertrophy. It is obvious that wide electrocardiographic variations will exist. However, we can distinguish, according to Peñaloza and co-workers[10] three principal types: slight pulmonary stenosis with a right systolic pressure less than 90 mm. Hg; moderate pulmonary stenosis with right ventricular systolic pressure between 90 and

130 mm. Hg; accentuated pulmonary stenosis with the right ventricular systolic pressure above 130 mm. Hg.

Cases with slight pulmonary stenosis: The tracing may be normal or with slight alterations. At times there is a discrete increase of R in V_1 without T changes and with a slight deviation of ÂQRS around +90° (Fig. 9). The cases whose ventricular systolic pressure closely approaches 90 mm. Hg may present the same electrocardiographic alterations which are found in moderate pulmonary stenosis.

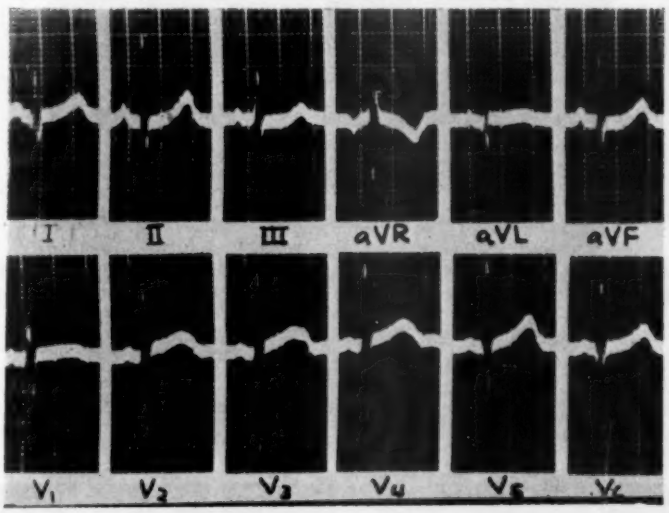

Fig. 9.—Pulmonary stenosis with right ventricular systolic pressure under 90 mm. Hg. The tracing shows very few changes as there is a slight increase in the voltage of R in V_1.

Cases with moderate pulmonary stenosis: The R wave is elevated in V_1 and the QRS complex is essentially positive. The T wave is almost always positive (Fig. 10). These changes are equal to those earlier described as characteristic of right ventricular hypertrophy with systolic overloading. They are found in V_1 and in other chest leads to the right of V_1 and are only exceptionally found in V_2 and V_3. The ÂQRS is located around +100°.

Cases with accentuated pulmonary stenosis: In the great majority of tracings the systolic pressure of the right ventricle was not higher than 150 mm. Hg. Only in one case did it reach 234 mm. Hg (Fig. 11). Also the electrocardiographic picture of right ventricular hypertrophy with systolic overloading is found (qR, Rs, rR, R complexes), but more frequently these morphologies are recorded in a greater number of chest leads to the right as well as to the left of V_1 (V_1 through V_3). In general, the voltage of the complexes is greater than in the former group. In the left leads the QRS complexes show a frank negativity. The T wave in V_1 and other right precordial leads is flattened or negative, and in extreme cases is of the ischemic type (Fig. 11). The deviation of ÂQRS to the right is considerable even though it does not reach the superior sextants of the frontal plane. At the same time the ÂT deviates to the left in opposition to the ÂQRS.[10]

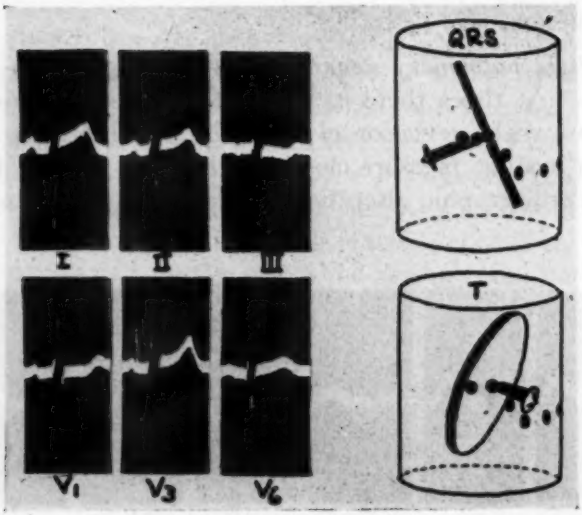

Fig. 10.—Pulmonary stenosis with right ventricular systolic pressure between 90 and 130 mm. Hg. The tracings show signs of right ventricular hypertrophy with systolic overloading of the right ventricle.

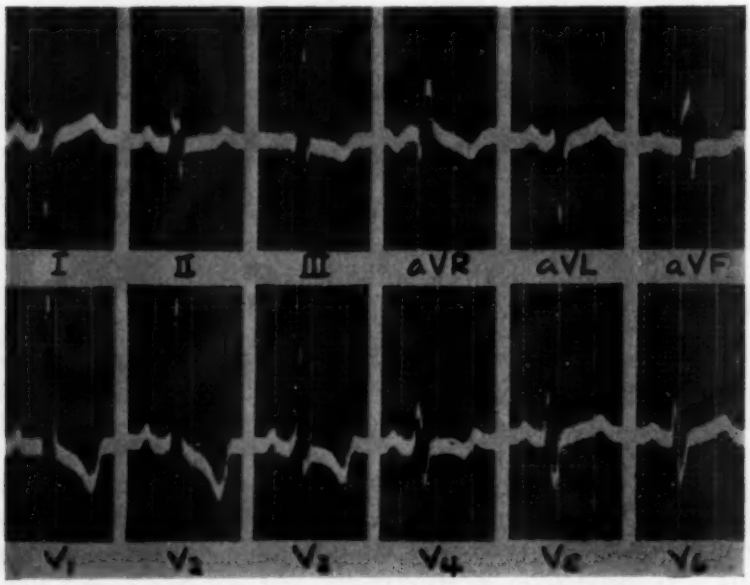

Fig. 11.—Pulmonary stenosis with right ventricular systolic pressure above 130 mm. Hg. The tracing shows signs of right ventricular hypertrophy with systolic overloading of the right ventricle. The T waves from V_1 through V_3 are of the ischemic type.

Pulmonary stenosis with atrial septal defect (trilogy of Fallot): In Fallot's trilogy we can consider, as in pure pulmonary stenosis, three different grades. These will depend upon the narrowness of the valvular orifice.

Grade 1. With systolic pressure in the right ventricle less than 90 mm.Hg

Grade 2. With a right systolic ventricular pressure between 90 and 130 mm. Hg

Grade 3. With a right systolic ventricular pressure above 130 mm. Hg (Fig. 12)

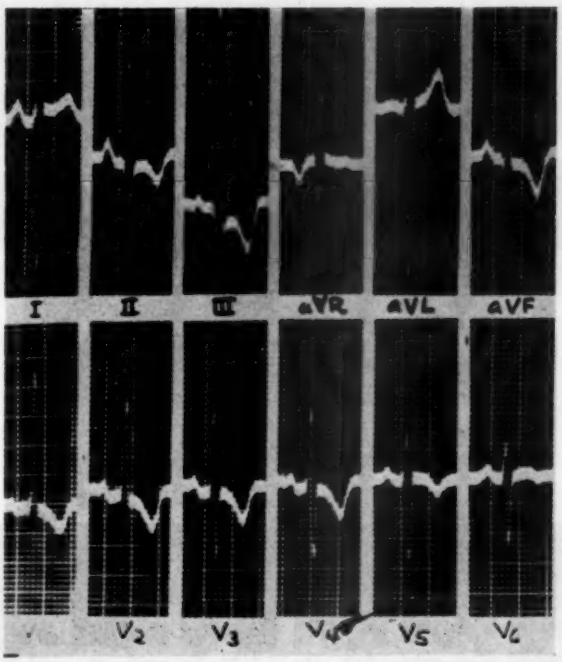

Fig. 12.—Pulmonary stenosis with atrial septal defect. The tracings show signs of right ventricular hypertrophy with systolic overloading of the right ventricle. The T waves from V_1 through V_5 are of the ischemic type.

There is a predominance of cases in Group 2 with a few in Groups 1 and 3. Thus, it is rare that a trilogy of Fallot will present a right ventricular systolic pressure less than 90 mm. Hg. We believe that this can be explained as follows: when there is a slight pulmonary stenosis with an anatomically but not physiologically patent foramen ovale a true trilogy of Fallot may be established when the systolic pressure of the right ventricle is sufficiently elevated. This in turn tends to increase the right ventricular diastolic pressure which consequently gives rise to an increased pressure in the right atrium. This cavity enlarges and a shunt from right to left may be established. Thus, a moderate pulmonary stenosis with a nonfunctional foramen ovale is potentially a trilogy of Fallot. When there is left-to-right atrial shunt we have to admit the existence of the interatrial foramen primum or secundum. If the atrial septum is normal and the valve of the foramen ovale has not fused, the shunt will be from right to left.

From the electrocardiographic point of view the picture is similar to pure pulmonary stenosis.

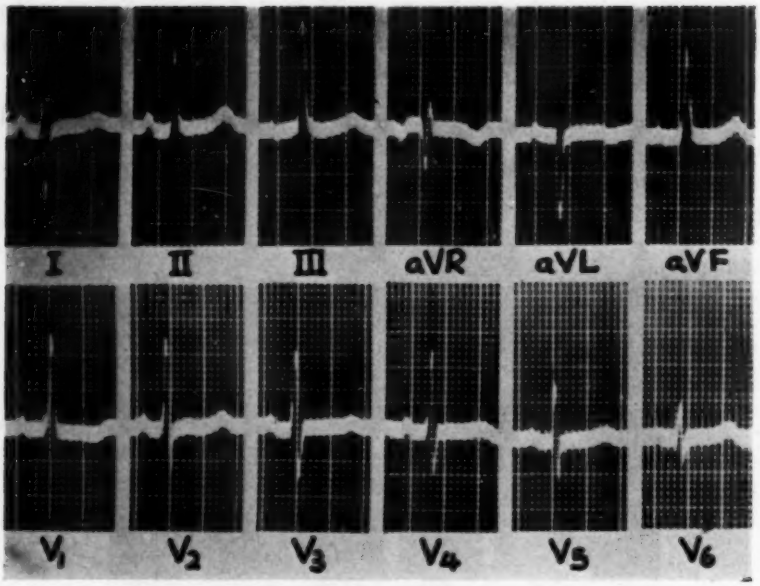

Fig. 13.—Tetralogy of Fallot. The tracings suggest right ventricular hypertrophy with systolic overloading of the right ventricle.

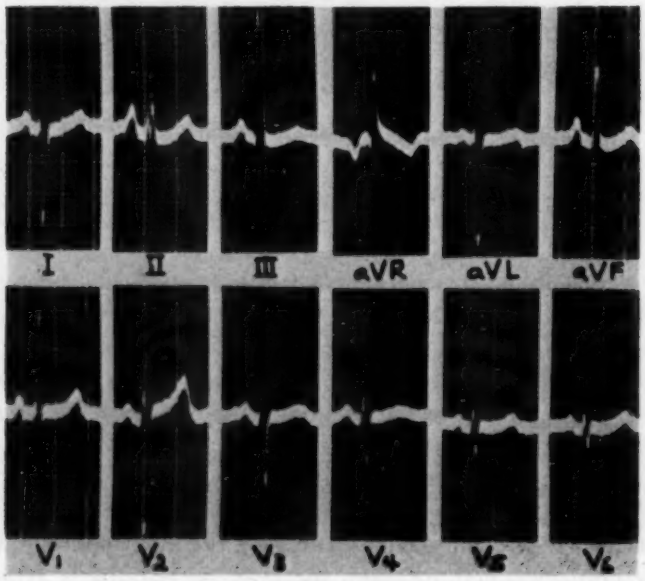

Fig. 14.—Pentalogy of Fallot. The tracings suggest right ventricular hypertrophy with systolic overloading of the right ventricle.

Tetralogy and pentalogy of Fallot (tetralogy plus atrial septal defect): An overriding aorta (Figs. 13 and 14) tends to equalize the two ventricular pressures. Therefore, these cases behave as pure pulmonary stenosis or as a trilogy with a moderate systolic hypertension of the right ventricle. The ÂQRS in this group, contrary to the previous groups, frequently was found in the right superior sextants of the frontal plane. In a few cases the tracings were suggestive of incomplete or complete right bundle branch block.

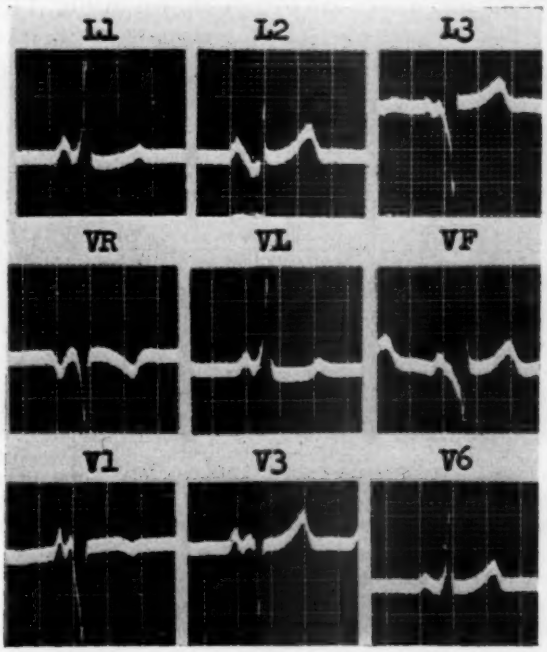

Fig. 15.—Ebstein's disease. The tracing shows Wolff-Parkinson-White syndrome type B (morphology similar to left bundle branch block).

5. *Ebstein's Disease.*—The majority of the authors are in agreement that the most characteristic electrocardiographic signs of this condition are incomplete or complete right bundle branch block and paroxysmal ventricular premature beats. A peaked P wave with an increased duration in Lead II and Lead III may also be found.[11] The great hypertrophy of the right atrium explains the right bundle branch block with a deep Q wave in the right and at times in the left, precordial leads.[12] Auricular flutter or fibrillation, as well as QR complexes in all the precordial leads, may be explained by this same huge right atrium.[13]

Recently, we have studied five cases of Ebstein's anomaly (two from the literature)[14-16] with Wolff-Parkinson-White syndrome type B.[13] We believe that the presence of this syndrome (Fig. 15) in a patient with suspected congenital heart obligates one to think of Ebstein's disease.

Accepting the fact that some muscle fibers situated above the tricuspid valve correspond, in reality, to ventricular muscle we thought intra-atrial tracings

should have a different morphology in the superior portion as compared to those of the inferior portion of the right atrial cavity. This was shown to be the case in a tracing obtained above the tricuspid valve which demonstrated a monophasic ventricular wave (Fig. 16). This was similar to those which are obtained in the dog due to the pressure of the exploring electrode on the ventricular muscle. When the electrode is compressing the auricular musculature a monophasic auricular wave is recorded. In this ventricular complex is superimposed the monophasic action potential of the auricle. The differences between auricular and ventricular monophasic waves are clearly shown in Fig. 17.

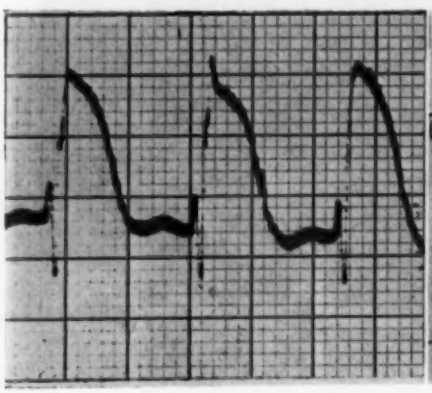

Fig. 16.

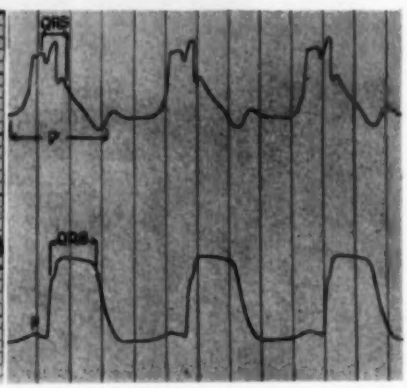

Fig. 17.

Fig. 16.—Monophasic ventricular waves obtained above the tricuspid valve in a case of Ebstein's disease.

Fig. 17.—Differences between auricular (upper tracing) and ventricular (lower tracing) monophasic waves.

Catheterization studies may suggest a tetralogy of Fallot when in reality we are dealing with Ebstein's disease. Soulié described[15] a case in which such a diagnostic confusion was presented, and the patient was operated upon for pulmonary stenosis. The patient died, and the necropsy demonstrated the existence of Ebstein's disease. This same error would have been committed in one of our cases if the intracavitary readings had not showed a monophasic ventricular wave in the lower portion of the right atrium. Therefore we must admit that an intra-atrial recording above the tricuspid valve may aid us to diagnose Ebstein's disease.

6. *Tricuspid Atresia.*—We do not discuss tricuspid atresia because its electrocardiographic patterns are well known, and we have nothing new to add.

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EXPERIMENTAL STUDIES ON ARRHYTHMIAS CAUSED BY FOCAL COOLING OF THE HEART

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EXPOSURE of human beings to cold may lead to the appearance of auricular fibrillation.[3,14,16] In experiments in which general hypothermia was produced, cardiac arrhythmias appeared in 70 per cent of the animals.[1] Auricular fibrillation is common with rectal temperatures of 29 to 31°, and ventricular fibrillation is likely with rectal temperatures below 26° Celsius.

An increasing number of patients with heart disease are being successfully operated upon under general hypothermia. This method has the advantage of diminishing the oxygen requirements of the heart to such a degree as to permit temporary interruption of the coronary blood supply; however, this method enhances the danger of ventricular fibrillation, and every surgeon using it has encountered such incidences. The mechanism of this form of ventricular fibrillation and the reason for its appearance are unknown.

In a previous report, it was shown that focal cooling of the exposed ventricle of a dog during auricular flutter or fibrillation leads to ventricular fibrillation within a few seconds whenever the ventricular rate is rapid. In one experiment, ventricular fibrillation appeared after only 6.8 seconds of cooling. On the other hand, ventricular fibrillation appeared rarely when cooling was performed during slow sinus rhythm, but extrasystoles were common. Conduction disturbances also were observed.[11]

These investigations were continued in order to study the effect of cooling on fibrillation of the auricles and to determine the influence of the ventricular rate on the appearance of ventricular fibrillation. In addition, the effect of preventive measures such as pretreatment with atropine or quinidine was explored.

METHOD

The experiments were performed on 33 dogs and 24 cats. The technic was the same as discussed in the previous report; the dogs received 1 ml. of Nembutal per 3 kilograms of body weight, intraperitoneally. In some of the experiments, the vagi were severed in the neck, while in others they were left intact. The electrocardiograms were usually registered in Lead I, rarely in Lead II. The

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cats received 1 ml. of Nembutal intraperitoneally, and the vagi were always left intact. In all experiments, the cooling was performed with standard test tubes filled with crushed ice. The test tube was applied to the heart without any pressure, and the cooled area was never greater than one square centimeter.

RESULTS

Cooling of the Auricles and Auricular Fibrillation.—Cooling of the auricles during the presence of auricular flutter or auricular fibrillation induced by focal application of aconitine has been used extensively in the course of our studies on the mechanism of these arrhythmias.[10] It was demonstrated that both these arrhythmias could be abolished immediately by cooling the area to which aconitine had been applied and that interruption of the cooling was followed by reappearance of the flutter or fibrillation. It therefore seemed justified to assume that these two arrhythmias originate in the focus created by the application of aconitine.

With this method of focal cooling, auricular flutter could be stopped at will.[10] This was also true of auricular fibrillation, but in this disturbance, the cooling of the area to which aconitine had been applied successfully interrupted the arrhythmia only during the first few minutes of its development. After that time, as well as when aconitine was spread over a large area of the auricle or was administered intravenously, focal cooling did not stop the fibrillation. Similarly, auricular fibrillation caused by faradic stimulation of the auricles or by pilocarpine or acetylcholine was not affected by focal cooling. In all these cases, it was necessary to cool the whole length of the sinus node as well as the A-V node simultaneously in order to re-elicit sinus rhythm.[12] It is to be expected that with diffusion of aconitine over the auricles or with systemic administration of this substance, many active centers are created, and that therefore the cooling of only one focus will not abolish the fibrillation. The hypothesis was also advanced that when one center forms frequent impulses for some time, this center will induce impulse formation in other centers[13] and result in several active centers. Thus, there exist two forms of auricular fibrillation which can be differentiated by cooling, one originating in a single focus and another sustained by several centers, but both presenting the same electrocardiographic picture.

Cooling during sinus rhythm: Since focal cooling of the ventricles in the course of a rapid rate regularly led to ventricular fibrillation, we investigated the response of the auricles to cooling under similar conditions.

Prolonged cooling (up to 20 minutes) of the body of the right auricle including the area of the sinus node or restricted to areas remote from the sinus node during sinus rhythm was without effect in nine out of ten experiments. Auricular fibrillation occurred in only one experiment and lasted for a few seconds after cooling was discontinued. In one experiment auricular fibrillation could not be induced by cooling alone; however, it was repeatedly elicited when the auricular wall was stretched during the cooling. Focal cooling remained ineffectual even when the auricles were electrically driven at rates up to 250.

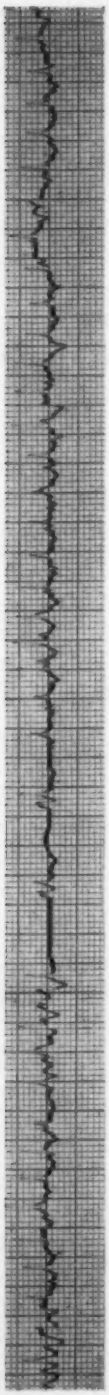

Fig. 1.—Auricular fibrillation was induced in a dog by focal application of aconitine on the appendix of the left auricle. Cooling of the right auricle stopped the fibrillation. The cooling was immediately discontinued. After two sinus beats the fibrillation reappeared.

Auricular fibrillation appeared twice during cooling of the right ventricle.

Cooling during fibrillation: In the preceding communication[11] the disappearance of auricular flutter or fibrillation during the cooling of the ventricles was reported. This interesting and unexplained phenomenon was often seen in the present series of experiments. It is clear that this is not a coincidence as the flutter or fibrillation reappeared a few seconds after the cooling was discontinued.

Because focal cooling of the ventricle could abolish auricular fibrillation, we investigated the effect of cooling of the fibrillating auricles at a distance from the sustaining focus. Auricular fibrillation was produced by the application of aconitine on the appendix of the left auricle, and the cooling thermode was placed on the wall of the right auricle far from the sinus node.

In five out of nine such experiments, the cooling stopped the fibrillation; the earliest response appeared after 36 seconds of cooling and the latest (in a cat) after 2 minutes and 5 seconds. Interruption of the cooling led to the immediate reappearance of the arrhythmia (Fig. 1). In all five successful experiments, the cooling was effective only during the first minutes after the establishment of the aconitine-induced fibrillation. It was ineffective later in the experiments, although several times the cooling period was extended for many minutes (up to 14 minutes and 40 seconds).

In the experiment of Nov. 17, 1953, on a cat, fibrillation stopped after 1 minute 10 seconds of the first cooling. A little later in the course of the same experiment, however, cooling for over 10 minutes had no effect. In another cat (Nov. 10, 1953), sinus rhythm was temporarily restored after only 45 seconds. Later on, the same area was cooled on five different occasions for 6 to 7 minutes, each time with no effect on the fibrillation.

The fact that auricular fibrillation induced by focal application of aconitine usually persists for over an hour and the observation that in these experiments fibrillation recurred a few seconds after cooling was stopped can be interpreted as proof that focal cooling of the auricle distant from the active center may abolish the fibrillation. This does not invalidate the previous experiments on the mechanism of auricular fibrillation, since in those experiments the cooling thermode was placed precisely on the area to which the aconitine had been applied and led to the immediate suppression of the fibrillation.

Atrioventricular Block and Intraventricular Block Induced by Focal Cooling.— An interesting phenomenon was the appearance of A-V block during the focal cooling of the ventricular surface. In the previous report we discussed the temporary appearance of a prolonged P-R interval and an increased A-V block in auricular flutter in the course of focal cooling of the ventricular surface. In the present experiments A-V block was frequent, and intraventricular block was observed in two dogs and in ten cats.

Fig. 2 illustrates such an experiment in a dog. Aconitine fibrillation was induced; cooling of the body of the right and left auricles did not affect it. The animal weighed 13 kilograms and received 2 mg. of atropine intravenously with a resultant sinus tachycardia. Cooling of the right ventricle caused ventricular

extrasystoles, prolongation of the P-R interval as well as sinus arrhythmia and right bundle branch block (Fig. 2,*C*). Ten minutes later, an area near the apex of the left ventricle was cooled; this caused a left bundle branch block to appear after 5 minutes and 3 seconds, and a marked A-V block after 6 minutes and 32 seconds.

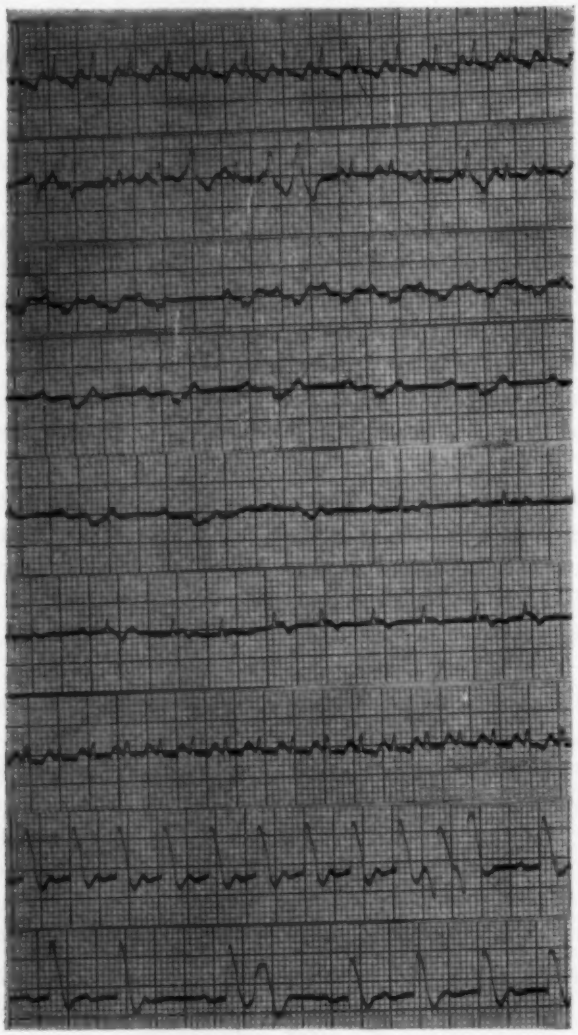

Fig. 2.—*A* shows a sinus tachycardia with a rate of 230 per minute, after the injection of 2 mg. of atropine. *B* was obtained after cooling of the right ventricle lasting 135 seconds; numerous ventricular extrasystoles, originating in both ventricles, appeared. When the cooling was repeated and continued for 185 seconds a prolongation of the P-R interval with a sinus arrhythmia and right bundle branch block were registered (*C*). *D* was registered after cooling for 256 seconds and shows a 2:1 A-V block with right bundle branch block. *E* and *F* show the rapid disappearance of the block a few seconds after discontinuation of the cooling. *G* was obtained 5 minutes later and shows the same electrocardiogram as *A*. Ten minutes after discontinuation of the cooling of the right ventricle the supra-apical area of the left ventricle was cooled. Left bundle branch block was registered after 303 seconds of cooling (*H*) and periodically dropped beats appeared after cooling for 392 seconds (*I*). All tracings were taken in Lead I.

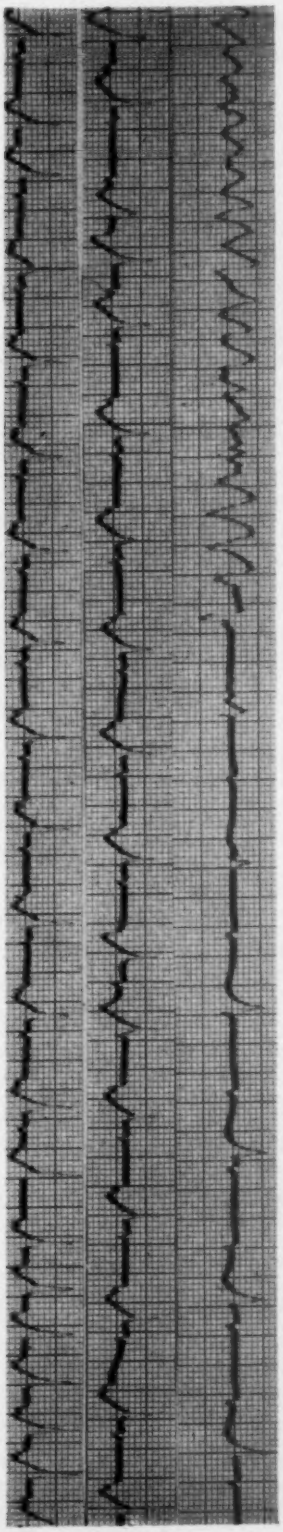

Fig. 3.—Experiment of Dec. 22, 1953, on a cat. Cooling of the right ventricle caused intraventricular block (*A*) with Wenckebach periods. A 2:1 block appears (*B*) and the block finally becomes complete (*C*). Suddenly, during the A-V block ventricular fibrillation sets in (*C*). Total duration of cooling, 3 minutes. All tracings in Lead I.

In the cat, A-V block was observed as early as 25 seconds after the beginning of the cooling, and this happened not only during tachycardia but also during sinus rhythm. Fig. 3 shows an intraventricular block with widening and slurring of the QRS complexes, and A-V block beginning with a prolongation of the P-R interval and ending with a complete dissociation between auricles and ventricles.

Fig. 4 illustrates the appearance of A-V block in another cat during sinus rhythm and during an electrically induced tachycardia.

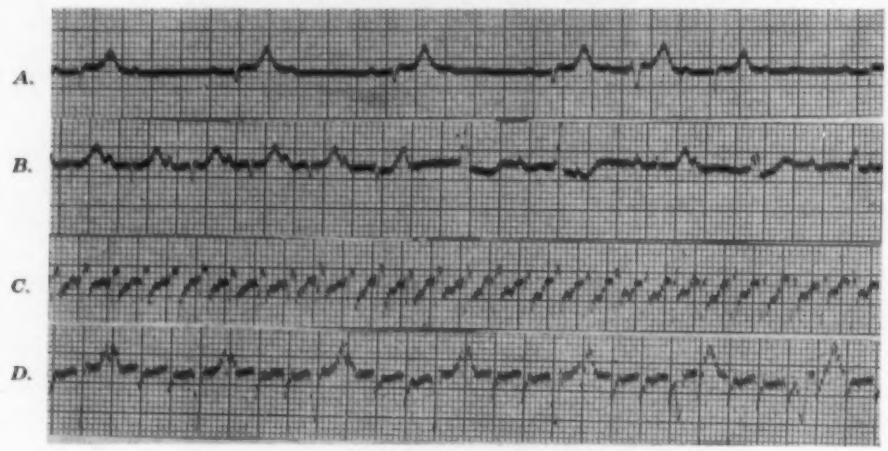

Fig. 4.—Experiment of Jan. 5, 1954, on a cat. Marked sinus bradycardia and A-V block had appeared after cooling of the right ventricle for 3 minutes (*A*). One milligram of atropine was injected intravenously and the left ventricle was cooled; *B* shows the beginning of A-V block with ectopic ventricular beats after 76 seconds of cooling. *C* shows a tachycardia of 300 elicited by electrical stimulation of the right auricle. Cooling of the right ventricle caused a complete A-V block after 36 seconds.

Frequent occurrence of A-V block in the cat led to a slowing of the ventricular rate and therefore prevented the appearance of ventricular fibrillation induced by cooling. Thus, in the experiment of Dec. 8, 1953, on a cat, the auricles were electrically stimulated at rates of 180, 250, 300, 375, and 500 per minute. In every instance, cooling of the ventricles caused an A-V block and no ventricular fibrillation appeared, although cooling was continued on one occasion for 10 minutes and 10 seconds. In the dog, severing the vagi had no influence on the appearance of the A-V block.

Extrasystoles and Paroxysmal Tachycardias Elicited by Cooling.—In the present series of experiments, cooling of the ventricles led in almost all instances to the appearance of extrasystoles. These were invariably ventricular extrasystoles. Auricular extrasystoles were never seen during cooling of either the auricles or the ventricles.

In three experiments, ventricular bigeminy occurred (Fig. 7). It developed only after prolonged cooling, stopped after cessation of cooling and could be re-elicited by cooling again. Therefore, there could be no question about the relation between the cooling and the bigeminal rhythm. Occasionally, extrasystoles appeared only during the cooling of the right ventricle and could not be elicited by cooling the left ventricle.

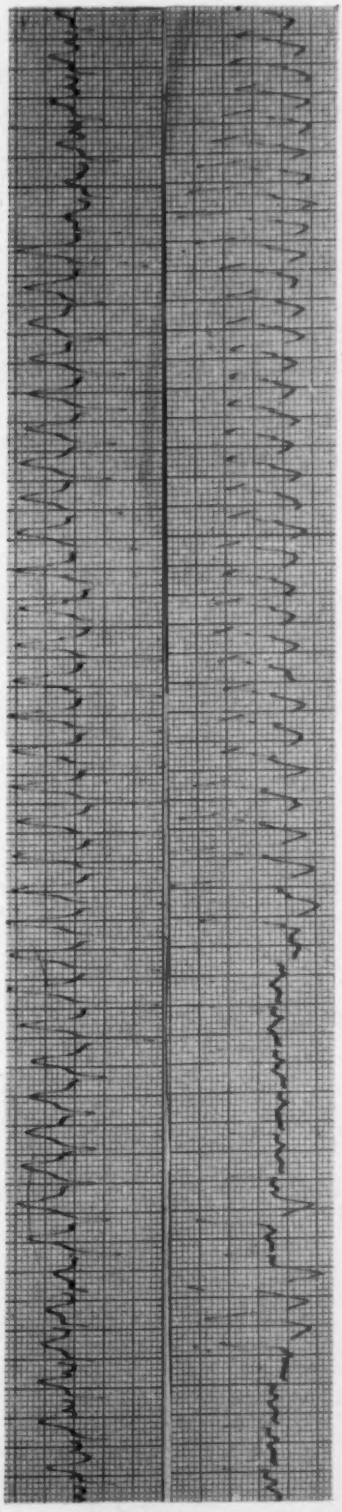

Fig. 5.—Experiments on dogs. Paroxysmal left and right ventricular tachycardias after cooling of the left and right ventricles, respectively. The dogs had received 2 mg. of atropine intravenously. Lead II.

Fig. 6.—*A* was obtained in an experiment on a dog (June 23, 1953). Cooling of the conus area of the right ventricle leads to the appearance of right and left ventricular extrasystoles and finally to a ventricular tachycardia and ventricular fibrillation. The animal had received 2 mg. of atropine sulfate. Total cooling period, 135 seconds. *B* was registered on Oct. 27, 1953. The dog had received 2 mg. of atropine and ventricular fibrillation appeared after cooling of the left ventricle for 3 minutes. Lead II.

The extrasystoles originated most often in the cooled ventricle, but as shown in the previous report,[11] they frequently appeared in the contralateral ventricle (Fig. 6).

They were particularly frequent in the atropinized animals in which ventricular fibrillation could be elicited only after prolonged cooling during rapid ventricular rates; paroxysmal ventricular tachycardias were quite frequent (Figs. 5 and 6) and showed great regularity extending over several hundred beats.

Ventricular Fibrillation and Cooling.—In these experiments, cooling during sinus rhythm or bradycardia during A-V block (Fig. 3) caused ventricular fibrillation only twice. In one experiment, fibrillation appeared 3 seconds after discontinuation of the cooling.

McWilliam found that cooling of the abdomen also leads to ventricular fibrillation.[5] We did not encounter this in the course of two experiments on the dog and three experiments on the cat, each of which extended for 20 minutes. Similarly, cooling of the pulmonary artery was without effect.

It may be considered that the various distal effects of cooling, namely, the influence of cooling the ventricle on the auricular rhythm, the appearance of arrhythmias in the contralateral ventricle, and the appearance of bradycardia and block may be due to cooling of the blood. Although it seemed very improbable that focal cooling of the ventricles could lead to a perceptible decrease in blood temperature, particularly when the effects were observed within a few seconds, in five experiments we registered the temperature within the right ventricle during the cooling by means of a thermocouple. In two experiments, no changes of temperature were noted within the heart although the usual electrocardiographic changes were present. In three other experiments there was a drop of 1° F., but no change in rhythm was seen at that time. The observation that even prolonged cooling of the thin-walled auricles or the pulmonary artery in the course of auricular fibrillation never causes ventricular fibrillation, whereas this arrhythmia was often seen after only a few seconds when the ventricles were cooled, also indicates that the responsible factor is not cooling of the blood.

Our investigations clearly demonstrate the relation between the existing ventricular rate and the appearance of ventricular fibrillation. It can be stated that the faster the ventricular rate, the shorter the cooling time necessary to elicit ventricular fibrillation.

This conclusion is based on experiments such as the one of Jan. 12, 1954, in a cat. The right ventricle was cooled for 7 minutes during sinus rhythm without any change of rhythm. Then, the auricles were stimulated electrically at a rate of 250 per minute and cooling of the same area, as previously, led to A-V block in 40 seconds. Later, the right ventricle was again cooled both during sinus rhythm and stimulation of the auricles at 250 per minute, and in each instance again led to an A-V block. When the left ventricle was cooled for 5 minutes during sinus rhythm no changes occurred. The auricles then were stimulated, as described previously, and ventricular fibrillation appeared after cooling of the left ventricle for 1 minute and 55 seconds. After sinus rhythm had been restored, cooling of the right ventricle on two more occasions again led to A-V block. The left ventricle was cooled four more times: once during sinus rhythm, cooling for 3 minutes caused no change in rhythm; during an

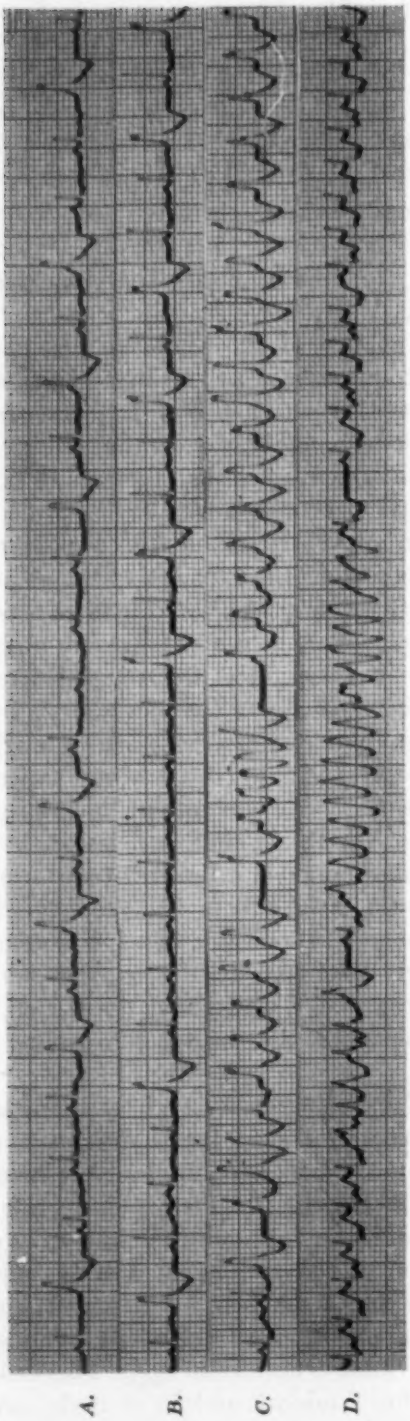

Fig. 7.—Cooling of the right ventricle was performed on a dog, after severing both vagus nerves in the neck. Cooling caused the appearance of ventricular bigeminy (Lead II); cooling was repeated twice with the same result (*A*). *B*, *C*, and *D* show the effect of cooling in an experiment on a dog on Sept. 22, 1953. Here 2 mg. of atropine had been given and cooling of the right ventricle caused, at first, bigeminal rhythm (*B*) and then multiple extrasystoles and prefibrillatory arrhythmias.

auricular tachycardia of 180 due to electrical stimulation of the auricles, ventricular fibrillation occurred in 45 seconds and when the auricular rate was increased to 250, the fibrillation developed once after 45 seconds and once after 53 seconds.

Thus, in this experiment cooling of the right ventricle failed to elicit ventricular fibrillation during sinus rhythm as well as during auricular tachycardia. This is not unusual during sinus rhythm, but the fact that fibrillation did not occur during the auricular tachycardias is due to the appearance of the A-V block every time cooling was performed; this prevented rapid ventricular rates. Cooling of the left ventricle produced no change during sinus rhythm, and, because no A-V block appeared during the auricular tachycardias, ventricular fibrillation developed in each instance in less than one minute.

Table I illustrates the results of some other experiments. It is evident that with higher ventricular rates, fibrillation appeared regularly and rapidly, while with lower rates it was often absent even during prolonged cooling.

TABLE I*

DATE	RATE	DURATION OF COOLING (SECONDS)	RESULT
Dogs			
1/19/1954	140	310	0
	181	120	0
	181	420	0
	214	95	Ventricular fibrillation
1/ 5/1954	250	103	0
	214	95	0
	300	65	Ventricular fibrillation
9/29/1953	214	270	0
	214	270	0
	300	180	Ventricular fibrillation
2/23/1953	115	145	0
	115	240	0
	115	315	0
	300	11	Ventricular fibrillation
3/ 9/1954	250	180	0
	250	225	0
	300	20	Ventricular fibrillation
Cats			
12/15/1953	230	670	0
	300	18	Ventricular fibrillation
	200	240	0
	280	45	Ventricular fibrillation
	250	33	Ventricular fibrillation
4/24/1954	250	300	0
	214	300	0
	360	10	Ventricular fibrillation

*This table shows in experiments on dogs and cats that with higher ventricular rates cooling provokes ventricular fibrillation readily, while prolonged cooling with slower rates is not followed by fibrillation.

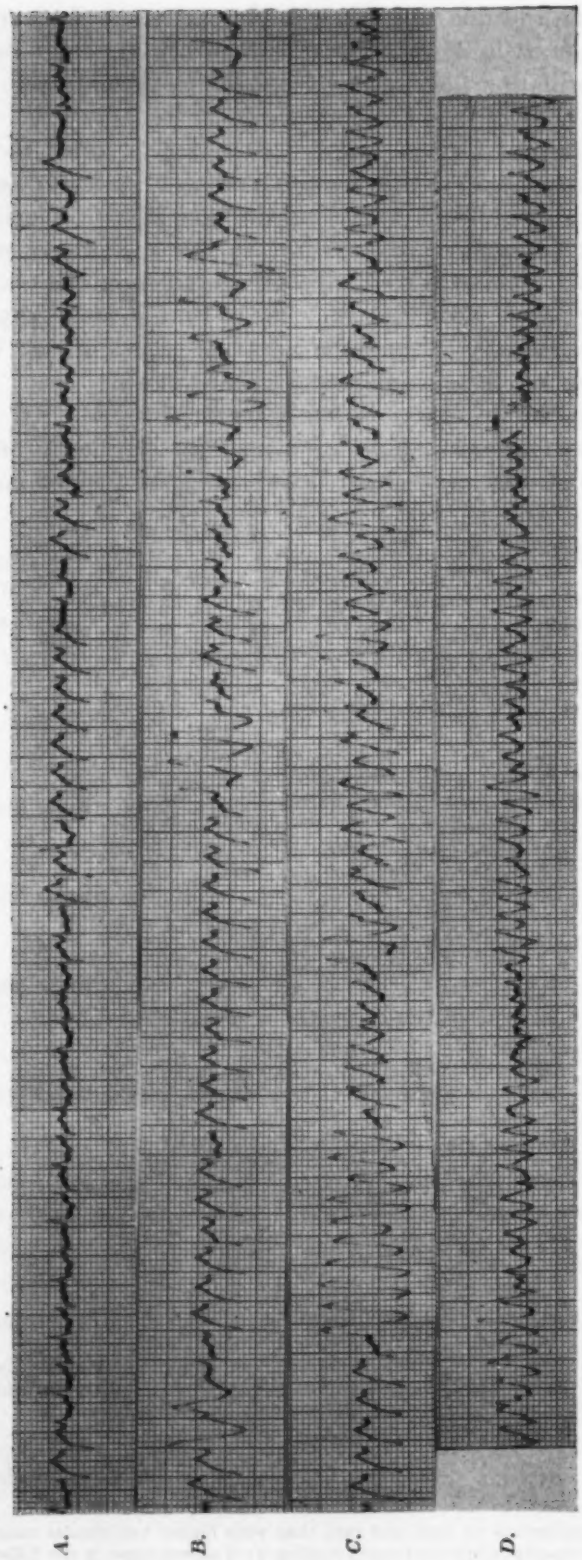

Fig. 8.—Experiment of May 18, 1954, on a dog weighing 11 kilograms, Lead I. The right auricle was stimulated electrically at a rate of 325 per minute, after an injection of 200 mg. of quinidine intravenously. Fibrillation appeared after 85 seconds of cooling. Fig. 8 shows the electrocardiogram just before the appearance of fibrillation. The strips are continuous. Some of the abnormal beats are ectopic beats, but an intraventricular block cannot be ruled out in others. At the beginning of the third strip (*C*) ventricular tachycardia sets in, originating in several centers and very slowly and gradually leading to ventricular fibrillation.

In the cat, the tachycardia present during the aconitine-induced auricular fibrillation was not rapid enough to produce ventricular fibrillation on cooling. It was necessary to produce higher rates by electrical stimulation.

As was stated previously, the appearance of A-V block by cooling, while rapid auricular rates were present, prevented the formation of ventricular fibrillation. In all these experiments, cooling during direct electrical stimulation of the ventricles at rates greater than 250 invariably led to ventricular fibrillation within a few seconds.

These experiments do not help to decide the question as to whether ventricular fibrillation is caused by a circus movement or by ectopic impulse formation. The hypothesis has been put forward[13] that rapid intrinsic or extrinsic stimuli in the heart induce a number of centers to become active and form independent impulses leading to ventricular fibrillation. When specific fibers are bombarded by stimuli at a critical rate, they form rapid impulses themselves and fibrillation develops. This hypothesis is supported by Fig. 8 which shows that cooling of the right ventricle caused not only right but also some left ventricular extrasystoles, then a right ventricular tachycardia also followed by left extrasystoles, and finally by fibrillation.

Atropine.—Fourteen dogs were given 1 to 3 mg. of atropine sulfate intravenously depending on the size of the animal. This measure always abolished a pre-existing aconitine flutter or fibrillation and led to a sinus tachycardia with a rate of about 250 per minute.

Although the atropinized animals were not protected from ventricular fibrillation induced by cooling, the duration of the cooling had to be greatly increased and in many animals the rate of 250 was insufficient and electrical stimulation at greater rates was necessary before the focal cooling would induce the fibrillation. Whereas without atropine, at a rate of 250, ventricular fibrillation usually appeared after a few seconds of cooling; after atropine this period was frequently over 2 minutes unless the ventricular rate was increased to 300 or more. In addition, cooling after atropine brought out groups of extrasystoles and tachycardias which in nonatropinized animals would have immediately led to fibrillation.

Thus, in the experiment of Sept. 22, 1953 (Fig. 7) the dog had been given 2 mg. of atropine intravenously; the sinus rate was 250 per minute. Cooling of the right ventricle led to multiple ventricular extrasystoles and ventricular tachycardia but not to ventricular fibrillation. In Fig. 7, *C* a distinct prefibrillatory tachycardia appeared but even after prolonging the cooling for 3 minutes and 20 seconds, only extrasystoles and a sinus bradycardia developed. The same effect was noted during a sinus tachycardia of 300 (electrical stimulation) and during cooling of the left ventricle.

On the fourth cooling of the right ventricle in the course of an auricular tachycardia of 300, ventricular fibrillation appeared after 14 seconds.

In the experiment on Jan. 5, 1954, the dog received 3 mg. of atropine intravenously. Cooling of the right ventricle was performed four times, during a sinus rate of 220; the cooling lasted up to 4 minutes and 37 seconds and did not

provoke fibrillation. Cooling of the right ventricle during electrical stimulation of the auricles with a rate of 300 led to ventricular fibrillation in 75 seconds. In another experiment (May 4, 1954) the dog had received 2 mg. of atropine. This time cooling of the ventricles during a rate of 300 led to ventricular fibrillation in 7 seconds.

Quinidine.—The effect of quinidine was more pronounced than that of atropine. When 200 mg. of quinidine hydrochloride (Brewer) were injected intravenously in six dogs, it slowed the existing rate and abolished arrhythmias but did not cause widening of the QRS complexes. Cooling rapidly led to further slowing of the rate and block but never to ventricular fibrillation or even extrasystoles.

However, fibrillation did appear whenever the cooling was performed during rapid artificial stimulation.

Thus in the experiment of May 18, 1954, the dog weighing 11 kilograms had received 200 mg. of quinidine. Cooling was started and the auricles were stimulated at 325 per minute. Fibrillation occurred after 1 minute and 25 seconds of cooling. Fig. 8 shows the electrocardiogram just before the onset of fibrillation. The four strips are continuous. Many abnormal beats are present and may be due to aberrant conduction in the ventricles. They are soon followed by definite extrasystoles which increase in number until the fourth strip when fibrillation becomes evident. It can also be seen that the extrasystoles originate in both ventricles.

This slow, gradual development of fibrillation after a prolonged tachycardia is in contrast to the untreated heart in which fibrillation follows after the first few groups of extrasystoles. This tracing is characteristic of those obtained by cooling hearts pretreated with quinidine.

DISCUSSION

These experiments show that cooling of the right auricle in the course of flutter or fibrillation originating in the left auricle abolished the existing arrhythmia and restored sinus rhythm in five out of nine dogs. There is no doubt that cooling was responsible as discontinuation of the cooling led to the immediate reappearance of the arrhythmia; furthermore this effect could be elicited repeatedly within a few minutes during the same experiment. It has been shown that otherwise auricular flutter and fibrillation due to topical application of aconitine will persist for more than one hour. This result was not unexpected, as in a previous report we found that focal cooling of the ventricles may also occasionally abolish auricular arrhythmias. It is interesting to note that these results were obtained after severance of the vagi in the neck.

Cooling of the right auricle during sinus rhythm or an electrically induced tachycardia of 250 did not lead to flutter or fibrillation. This is in contrast to the common occurrence of auricular fibrillation during general hypothermia in man.

When auricular fibrillation was present, the effect of cooling described previously could be observed only at the beginning of this arrhythmia. Later

on, the attempts to stop the fibrillation by cooling an area of the auricle distant from the point of application of aconitine were not successful. This is also in keeping with previous results; when the aconitine fibrillation first forms, cooling of the focus of origin leads to immediate cessation of the fibrillation; after the fibrillation has continued for sometime, cooling of that same area will not abolish the arrhythmia. In order to stop it at this time, it was necessary to cool the sinus and the A-V nodes simultaneously. This fact has led to the assumption that the longer lasting fibrillations, although originating in one focus, set up other independent centers of rapidly forming stimuli.[13]

Another effect of cooling which manifested itself at a distance from the thermode was the appearance of A-V block and intraventricular block during the cooling of a small area of the ventricle. The A-V block appeared often in cats, and sometimes in dogs, even after the animal had received atropine. It is known that when the whole animal is refrigerated, there is prolongation of the A-V conduction time and widening of the QRS complex, as might be expected in view of the slowing of all functions due to cooling. However, in the present experiments, these changes appeared after cooling only a small area on the surface of the ventricle and in many cases after only a few seconds. Under these conditions it would have been unlikely to attribute them to a fall of the temperature of the blood; moreover, determination of the temperature of the intracardiac blood by means of a thermocouple revealed that these changes did in fact occur while the blood temperature remained unchanged.

A-V block during cooling acted protectively since it prevented a rapid ventricular activity in spite of the high auricular rate, thereby preventing the appearance of ventricular fibrillation. It is particularly interesting to note that in some experiments the A-V block appeared only when the right ventricle was cooled. No such effect was seen while the left ventricle was being cooled, and therefore ventricular fibrillation always occurred rapidly.

The appearance of A-V block and intraventricular block could be attributed to various intracardiac reflexes of which we know little at the present time. It is, however, difficult to account for these changes occurring even after atropinization. The observation of block in general hypothermia is easily understood. We are not able to explain the block in the present experiments following focal cooling. We lack knowledge concerning formation of acetylcholine during the cooling process.

It is much more difficult to establish ventricular fibrillation in the cat than in the dog. In cats, even prolonged ventricular cooling during aconitine-induced auricular fibrillation did not lead to ventricular fibrillation while this appeared regularly in the dog. However, when the ventricular rate was pushed to higher levels electrically in the cat, focal cooling invariably led to fibrillation.

In rare instances, in the dog, focal cooling induced ventricular fibrillation during sinus rhythm or in the presence of A-V block. Once, it even appeared during sinus rhythm 3 seconds after the cooling had been discontinued. It has been found that in the heart muscle of the dog, when the body temperature returns to normal after cooling, an abnormally short refractory period and a high

excitability appear.[6] This may explain the occurrence of fibrillation after cooling has been stopped which was also noted in our previous report.

Shortening of the refractory period associated with an increase in rate is a well-established physiologic phenomenon. In addition it has been shown that rapid stimulation of the heart awakens new foci of stimulus formation.[9] If one stimulus is applied, one extrasystole will appear provided the stimulus does not occur during the supernormal phase. However, when several stimuli are applied in rapid succession, there will develop longer chains of ectopic beats due to repetitive impulse formation. The experiments presented here show that the stimuli induced by cooling lead to the creation of new foci of impulse formation in the contralateral ventricle and support our contention that when these multiple centers reach a critical rate ventricular fibrillation occurs.

Atropine and quinidine clearly diminish the propensity of the heart to develop ventricular fibrillation by cooling during rapid ventricular rates, but even with these drugs, the appearance of fibrillation could not be prevented. However, the cooling time must be longer and the ventricular rates higher than in nontreated animals, and this permits the appearance of "prefibrillatory" ventricular tachycardias which otherwise are not seen.

These experiments confirmed the conclusion of our previous report, namely, that cooling of a focal area of the heart and the resulting increased lability and excitability lead as a purely local phenomenon to ectopic impulse formation. It is probable that in the heart muscle fiber, as in nerve, cooling increases the negative after-potential and the supernormal phase of excitability. The rheobase is diminished, and therefore the critical level of excitability is lower. The conditions for formation of impulses are very favorable, and therefore a weaker stimulus can, if acting long enough, elicit a response.[2] In the cooled muscle strip of the frog one electrical stimulus applied early during the refractory phase elicits not only a local "action phenomenon" that is a markedly shortened action current but this is followed by a second normal monophasic action current.[4]

The labile condition of the heart during cooling is demonstrated by the increased tendency to fibrillate when manipulated.[15]

The importance of the heart rate for the appearance of arrhythmias is also evident from experiments on the isolated rabbit heart. With temperatures under 27° C. rapid stimulation evoked paroxysmal tachycardias and fibrillation.[8]

It should be emphasized that there is a difference between experiments in which the whole heart is cooled and those in which only focal cooling is employed as in the present experiments. Cooling of the whole heart or focal cooling may abolish existing arrhythmias due to its inhibitory action on impulse formation.[7] Cooling, however, causes also physiologic changes which lead to formation of new impulses. In this double action it resembles potassium, digitalis, procaine, quinidine and other substances which can inhibit impulse formation but also may lead to arrhythmias.

SUMMARY

Focal cooling of the right auricle over a period of 20 minutes during sinus rhythm caused auricular fibrillation only once in ten experiments.

Cooling of the right auricle during auricular fibrillation caused by topical application of aconitine on the left auricle stopped the fibrillation five times in nine experiments. Cessation of the cooling led to the immediate reappearance of the fibrillation. This result was obtained only during the early phase of the aconitine-fibrillation.

Focal cooling of the ventricle frequently caused A-V block and intraventricular block in the cat but rarely caused these effects in the dog. In one experiment on the dog, cooling of the left ventricle induced left bundle branch block. The block appeared after severing both vagi in the neck as well as after atropinization of the animal. In some experiments it appeared only during cooling of the right ventricle but not during cooling of the left ventricle. A-V block was observed as early as 25 seconds after the beginning of the cooling.

The appearance of A-V block during focal cooling of the ventricles prevented high ventricular rates and therefore prevented the development of ventricular fibrillation.

Focal cooling provoked ventricular but not auricular extrasystoles. They originated not only in the cooled ventricle but also in the contralateral one. This was particularly the case during the prefibrillatory state; when the right ventricle was cooled and rapid right ventricular ectopic beats appeared, the tracings clearly show the presence of impulses being fired from the left ventricle. A bigeminal rhythm occurred during cooling but was rare. Not infrequently extrasystoles could be elicited by cooling the right ventricle but not by cooling the left. Extrasystoles in groups, multiple extrasystoles, and ventricular tachycardias were more common in the atropinized dog; this was due to the delay in onset of ventricular fibrillation following the use of this drug.

Ventricular fibrillation appeared in one experiment 3 seconds after discontinuation of the cooling.

Measurement of the intracardiac blood temperature with a thermocouple during cooling showed that the described changes appeared without any change in the temperature.

The experiments showed clearly that ventricular fibrillation appeared more readily with higher rates. Its appearance was delayed or prevented after administration of atropine and particularly quinidine, but with ventricular rates of 300 and above, focal cooling always elicited it.

After atropine and quinidine the duration of the prefibrillatory state was prolonged.

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THE CLINICAL ESTIMATION OF PULMONARY HYPERTENSION ACCOMPANYING MITRAL STENOSIS

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ONE of the major factors determining the desirability of mitral valve operation in patients with rheumatic mitral stenosis is the degree of pulmonary hypertension present. As is well known from previous writings,[1] rheumatic mitral stenosis may, at rest, be associated with pulmonary blood pressures varying from the normal mean of 12 to 17 mm. Hg to values exceeding those in the systemic circulation. Since we believe that not all patients with mitral stenosis need operation, the determination of the pulmonary blood pressure becomes important.

It is not always possible to rely on the patient's history for the evaluation of pulmonary hypertension. Restriction of activity accompanying mitral stenosis may be due to neurosis, bronchial asthma, pulmonary emphysema, active rheumatic carditis, paroxysmal auricular fibrillation, or thyrotoxicosis, as well as to mitral obstruction and pulmonary congestion, and hence is not always a dependable guide to the degree of pulmonary hypertension present.

Determination of the pulmonary blood pressure by direct measurement through cardiac venous catheterization is time consuming, expensive, and not without hazard. Four of our patients with rheumatic mitral stenosis and auricular fibrillation have developed small pulmonary emboli after cardiac catheterization. One who had sinus rhythm developed auricular fibrillation during the procedure. Although this arrhythmia reverted to sinus rhythm with quinidine, it later recurred and became permanent. Thus it would be helpful if routine catheterization of the heart could be avoided in patients who are potential candidates for mitral valvulotomy. This could be done if reliable clinical criteria could be found for estimating the degree of pulmonary hypertension.

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MATERIAL

The patients studied were from the Medical Service and Cardiac Clinic of the Brooklyn Hospital. Forty-five consecutive patients with rheumatic mitral valve disease were studied and form the basis of this report. Five of the forty-five were eliminated: one had peripheral signs of aortic stenosis; one had peripheral signs of aortic insufficiency; one had a thrill accompanying aortic stenosis; one had primarily mitral insufficiency; one was studied only following mitral commissurotomy. Of the forty patients remaining, thirty-one were women and nine were men.

METHODS

With regard to the clinical evidence of pulmonary hypertension, the following points were evaluated. In the history, a story of hemoptysis, paroxysmal nocturnal dyspnea, or right-sided heart failure was noted. In the physical examination, the intensity of the pulmonary second sound was evaluated. This was compared to the aortic second sound, realizing that occasionally there may be transmission of the pulmonary valve closure sound to the right of the sternum. However, it is believed that, because of variation in the amount of chest wall and lung between the pulmonary valve and the ear, intensity of the sound or palpability of pulmonic closure per se is of little help. The pulmonary second sound was considered to be slightly accentuated or one-plus when equal to the aortic second sound. Pulmonary closures slightly louder than this were graded two-plus, and quite loud closures as three-plus. The intensity of the apical diastolic murmur was also noted. Barely audible murmurs were graded one-plus; fairly loud murmurs as two-plus; fairly loud murmurs with a thrill were graded three-plus; very loud murmurs were graded four-plus. The Graham Steell murmur was not evaluated in this study because of the difficulty in distinguishing it from a mild aortic insufficiency murmur without peripheral signs. Left parasternal heaves due to right ventricular hypertrophy[2] were not routinely evaluated but were looked for in some patients and will be commented upon.

In the routine laboratory work, special attention was paid to the electrocardiogram and to the posteroanterior and oblique teleroentgenograms of the heart. The electrocardiogram was studied for evidence of right ventricular hypertrophy in three ways. In precordial Lead V_1, right ventricular hypertrophy was considered present if the R/S ratio exceeded unity and if the intrinsicoid deflection was 0.03 second or longer from the beginning of the QRS complex. If only one of these findings was present, the electrocardiogram was considered suggestive of right ventricular hypertrophy. The electrical axis was calculated by Dieuaide's chart; right-axis deviation was said to be present when the electrical axis exceeded 90 degrees. The axis-deviation index was also determined from Lead aV_L. The teleroentgenograms were studied as follows. In the posteroanterior view, the degree of dilatation of the left and main pulmonary arteries was graded from one- to four-plus. In the right anterior oblique view, the enlargement of the right ventricular outflow tract was graded from one- to four-plus. In the left anterior oblique view, the degree of enlarge-

ment of the right ventricular inflow tract was graded from one- to four-plus. Subjects with a total of three-plus or less from the three criteria were considered to have slight evidence of right ventricular and pulmonary arterial enlargement; a total of four- to six-plus was considered moderate, and seven-plus through nine-plus was considered marked enlargement. None exceeded nine-plus.

Cardiac venous catheterization was performed in the customary manner.[3] An attempt was made to secure a steady state by the use of mild sedation, familiarizing the patient with the apparatus, and stabilizing the pulse and respiration prior to measurements. Pressures were recorded by means of Sanborn electromanometers and Poly-Viso direct-writing electrocardiograph. Ten centimeters up from the patient's back was used as a zero point. Mean pressures were determined by planimetry.

Patients were classified into three groups according to the mean pulmonary arterial pressures. Those with pressures ranging from normal through 29 mm. Hg were considered to have no pulmonary hypertension or mild pulmonary hypertension. According to some authorities,[4] these patients might be considered undesirable candidates for commissurotomy. A second group comprised patients having mean pulmonary arterial pressures ranging from 30 to 49 mm. Hg. They were considered to have moderate pulmonary hypertension. According to some,[4] these patients may represent the ideal pressure level for consideration of operation, lying between the mild group, who may have insufficient mitral obstruction, and the severe group, who may have irreversible pulmonary vascular change. The third group comprised those whose mean pulmonary arterial pressures were 50 mm. Hg or more; this group was considered to have severe pulmonary hypertension.

In addition to measurement of pulmonary arterial pressures, record was also made of right atrial systolic pressure in those patients having sinus rhythm. This was done to evaluate the association of prominent "A" waves in the right atrial pulse or jugular venous pulse with right ventricular hypertension.

RESULTS

The results of these studies indicated are summarized in the tables, the patients being divided into the three groups of mild or no pulmonary hypertension, moderate pulmonary hypertension, and severe pulmonary hypertension as previously described. Eighteen patients, fourteen women and four men, fell into the group with mild or no pulmonary hypertension, their mean pulmonary arterial pressures varying from 11 to 29 mm. Hg (Table I). Three had normal resting pulmonary arterial pressure. Ten had moderate pulmonary hypertension, with mean pressures ranging from 30 to 49 mm. Hg (Table II). Nine of these were women. Twelve subjects were found to have severe pulmonary hypertension; their mean pulmonary arterial pressures ranged from 53 to 106 mm. Hg (Table III). Eight of these were women.

Individual manifestations in the three groups were found to be as follows:

1. *Right Atrial Systolic Pressure.*—Auricular fibrillation was present in 33⅓ per cent of the mild group, 60 per cent of the moderate group, and in 50

TABLE I. MILD OR NO PULMONARY HYPERTENSION: MEAN PRESSURE BELOW 30 MM. HG

PATIENT, AGE, SEX, DIAGNOSIS	PULMONARY ARTERIAL PRESSURE (MM. HG)	RIGHT ATRIAL SYSTOLIC PRESSURE (MM. HG)	RIGHT VENTRICULAR ENLARGEMENT (X-RAY)	RIGHT VENTRICULAR HYPERTROPHY (ECG)	RIGHT-AXIS DEVIATION (ECG)	INTENSITY OF APICAL DIASTOLIC MURMUR	PULMONARY SECOND SOUND	HEMOPTYSIS	RIGHT HEART FAILURE	PULMONARY EDEMA	AUTOPSY OR OPERATIVE FINDINGS; LONGEST DIAMETER MITRAL VALVE
1. F.D., 39, F. M.S.	17/9 11	7	None	None	None	+	Normal	+	0	0	—
2. L.G., 26, F. M.S.	24/9 13	5	Moderate	None	None	+++	+	0	0	0	10 mm. No M.I.
3. J.V., 30, F. M.S.	24/11 15	5	Slight	None	None	+++	+	0	0	0	—
4. M.H., 48, F. M.S., M.I., A.F.	29/13 18	—	Marked	None	None	+++	+	0	0	0	10 mm. No M.I.
5. J.P., 14, M. M.S.	28/10 18	8	Slight	None	None	+	+	0	0	0	—
6. C.Q., 36, F. M.S.	31/13 19	4	Marked	Suggestive	Yes	++	++	0	+*	0	—
7. M.F., 38, F. M.S., ?M.I.	33/12 20	9	Slight	None	None	+	Normal	0	0	0	—
8. D.A., 39, M. M.S.	35/14 22	8	Marked	None	Yes	+++	+	+	0	0	6 mm. No M.I.
9. T.B., 32, F. M.S.	32/19 23	—	Moderate	None	None	+++	Normal	0	0	0	—
10. C.M., 45, F. M.S., A.F.	36/17 26	—	Moderate	None	None	+++	+	0	?	0	7 mm. No M.I.

11. G.G., 42, M. M.S.	38/20 26	8	Slight	None	None	++	++	0	0	+	—
12. K.F., 37, F. M.S., A.F.	35/12 27	—	Moderate	None	None	+	?	0	+	+	—
13. M.T., 30, F. M.S.	38/19 28	15	Moderate	Suggestive	Yes	+++	++	+	+	0	8 mm. No M.I.
14. L.L., 24, F. M.S.	37/14 28	4	Moderate	None	None	+++	++	0	+	+	—
15. H.C., 39, F. M.S., M.I., A.F.	35/21 28	—	Moderate	None	None	+++	+	0	0	0	—
16. E.V., 21, M. M.S.	47/16 29	7	Moderate	None	None	++++	++	+	0	0	6-7 mm. No M.I.
17. R.K., 43, F. M.S., A.F.	45/20 29	—	Marked	Yes	Yes	++	+	0	+	0	—
18. I.C., 55, F. M.S., A.F.	40/19 29	—	Moderate	Suggestive	None	++	+++	0	0	0	10 mm. M.I. present

*Active carditis.

TABLE II. MODERATE PULMONARY HYPERTENSION: MEAN PRESSURE 30 TO 49 MM. HG

PATIENT, AGE, SEX, DIAGNOSIS	PULMONARY ARTERIAL PRESSURE (MM. HG)	RIGHT ATRIAL SYSTOLIC PRESSURE (MM. HG)	RIGHT VENTRICULAR ENLARGEMENT (X-RAY)	RIGHT VENTRICULAR HYPERTROPHY (ECG)	RIGHT-AXIS DEVIATION (ECG)	INTENSITY OF APICAL DIASTOLIC MURMUR	PULMONARY SECOND SOUND	HEMOPTYSIS	RIGHT HEART FAILURE	PULMONARY EDEMA	AUTOPSY OR OPERATIVE FINDINGS; LONGEST DIAMETER MITRAL VALVE
19. L.S., 27, F. M.S., M.I.	46/15 30	9	Marked	None	None	+++	++	0	0	0	—
20. A.N., 32, F. M.S.	42/25 34	4	Slight	None	None	++	++	0	+	0	12 mm. M.I. present
21. F.S., 41, F. M.S., T.I., A.F.	57/33 35	—	Marked	Yes	Yes	+	Normal	+	+	0	25 mm. × 2 m.
22. C.I., 49, F. M.S., M.I., A.F.	71/32 37	—	Marked	None	None	+++	++	0	+	0	—
23. E.M., 49, F. M.S., A.F.	56/23 37	—	Moderate	None	None	+	?	0	+	0	7 mm. No M.I.
24. B.D., 44, F. M.S., ?A.I., A.F.	59/29 42	—	Marked	Yes	Yes	+++	++	0	+	0	—
25. D.M., 27, M. M.S.	68/32 45	7	Moderate	Yes	Yes	+++	+++	+	+	0	6 mm. M.I. present
26. A.P., 36, F. M.S., M.I., T.S., A.S., A.I., A.F.	76/32 46	—	Marked	Yes	Yes	+++	++	0	+	0	4-5 mm. No M.I.
27. R.F., 39, F. M.S., A.F.	93/29 47	—	Marked	Yes	Yes	++	++	0	+	0	—
28. F.P., 36, F. M.S.	65/37 49	7	Marked	Suggestive	Yes	+++	++	0	0	0	5 mm. No M.I.

TABLE III. SEVERE PULMONARY HYPERTENSION: MEAN PRESSURE 50 MM. HG OR ABOVE

	PATIENT, AGE, SEX, DIAGNOSIS	PULMONARY ARTERIAL PRESSURE (MM. HG)	RIGHT ATRIAL SYSTOLIC PRESSURE (MM. HG)	RIGHT VENTRICULAR ENLARGEMENT (X-RAY)	RIGHT VENTRICULAR HYPERTROPHY (ECG)	RIGHT-AXIS DEVIATION (ECG)	INTENSITY OF APICAL DIASTOLIC MURMUR	PULMONARY SECOND SOUND	HEMOPTYSIS	RIGHT HEART FAILURE	PULMONARY EDEMA	AUTOPSY OR OPERATIVE FINDINGS; LONGEST DIAMETER MITRAL VALVE
29.	P.S., 52, M. M.S., A.F.	82/42 53	—	Marked	Yes	None	++	++	+	+	0	6-7 mm. No M.I.
30.	P.C., 36, F. M.S., ?A.I.	89/10*	—	Moderate	Yes	None	++	+	+	0	0	—
31.	M.N., 35, F. M.S., A.F.	70/45 56	—	Marked	Yes	No	++	++	0	+	0	? 4 mm.
32.	L.G., 30, F. M.S., M.I., A.F.	83/47 58	—	Marked	Yes	Yes	++	++	0	+	+	25 mm. M.I. present
33.	S.L., 37, F. M.S.	75/38 58	5	Moderate	Suggestive	No	+++	++	+	+	+	6-7 mm. No M.I.
34.	L.S., 47, M. M.S., M.I., T.I., A.F.	79/42 60	—	Marked	None (? Myocardial Infarction)	None	++++	++	0	+	0	—
35.	J.L., 32, M. M.S., M.I.	81/50 61	—	Marked	Suggestive	None	++	+	+	+	0	—
36.	R.W., 52, F. M.S., M.I., ?A.I., A.F.	95/44 62	—	Marked	Suggestive	Yes	++	+	0	+	0	1 finger M.I. present
37.	A.P., 39, F. M.S., M.I.	96/41 62	8	Moderate	Yes	Yes	+++	+++	+	+	+	6-7 mm. No M.I.
38.	F.D., 48, M. M.S.	121/47 73	8	Marked	Yes	Yes	+	+	+	+	0	6-7 mm. M.I. present
39.	C.K., 41, F. RHD, M.S., A.F.	120/56 78	—	Marked	Yes	Yes	+	+++	+	+	+	5-6 mm. No M.I.
40.	A.R., 35, F. RHD, M.S.	149/79 106	—	Marked	Yes	Yes	+++	+	0	+	+	7 mm. No M.I.

*Right ventricular pressure.

per cent of the severe group. Eight mm. Hg was considered to be the upper normal for right atrial systolic pressure.[5] Elevated right atrial systolic pressure was observed in two of eleven observations in the mild group; in one of four patients in the moderate group; and not in three of the severe group.

2. *Roentgen Evidence of Right Ventricular Hypertrophy.*—In the mild group there was none in one patient, slight in four, moderate in nine, and marked in four. In the moderate group, right ventricular hypertrophy was slight in one, moderate in two, and marked in seven. In the severe group, right ventricular hypertrophy was moderate in three patients and marked in nine.

3. *Electrocardiographic Studies.*—

a. *Evidence of right ventricular hypertrophy in precordial Lead V_1:* In the mild group, this was present in one subject and suggested in three. In the moderate group, right ventricular hypertrophy was present in five and suggested in one. In the severe group, right ventricular hypertrophy was present in eight and suggested in three. The only patient (L.S.) in the severe group lacking at least suggestive evidence of right ventricular hypertrophy had absent or diminutive R waves in all precordial leads, suggesting extensive old anterior infarction. All other patients with mean pulmonary arterial pressures above 42 mm. Hg had findings in Lead V_1 suggestive or indicative of right ventricular hypertrophy. Only one patient (C.Q.) having a mean pulmonary arterial pressure below 28 mm. Hg demonstrated this change; she had active rheumatic carditis.

b. *Right-axis deviation:* This was present in four of eighteen patients in the mild group; in six of ten in the moderate group; and in six of twelve in the severe group. This followed the changes of right ventricular hypertrophy in Lead V_1 fairly closely except in the severe group, where the precordial Lead V_1 indicated right ventricular enlargement more often.

c. *Axis-deviation index:* This exceeded minus 10 in one of eighteen subjects in the mild group; in four of ten in the moderate group; and in four of twelve in the severe group. This appeared to be the least sensitive of the three indices of right ventricular hypertrophy.

4. *Intensity of the Apical Diastolic Murmur.*—In the mild group, the murmur was faint in three, moderate in four, associated with a thrill in ten, and was very loud in one. Eleven of eighteen in this group, or 62 per cent, had a loud apical diastolic murmur. In the moderate group, the apical diastolic murmur was faint in two, moderate in two, and was associated with a thrill in six. Six of ten, or 60 per cent, had a loud diastolic apical murmur in this group. In the severe group, the apical diastolic murmur was faint in two, moderate in six, was associated with a thrill in three, and was very loud in one. Four of twelve, or 33⅓ per cent, in this group had loud apical diastolic murmurs.

5. *Intensity of the Pulmonary Second Sound.*—In the mild group, P_2 was normal in three, slightly accentuated in seven, moderately accentuated in five, and loud in one. In the last, mean pulmonary arterial pressure was 29 mm. Hg. In the moderate group, P_2 was normal in one, moderately accentuated in seven,

and loud in one. In the severe group, P_2 was slightly accentuated in five, moderately accentuated in five, and loud in two.

6. *Hemoptysis.*—This complication was present in four of eighteen subjects in the mild group, in two of ten in the moderate group, and in seven of twelve in the severe group (58 per cent).

7. *Right Heart Failure.*—This was found in five of seventeen patients in the mild group (29 per cent), in eight of ten in the moderate group (80 per cent), and in eleven of twelve in the severe group (92 per cent).

8. *Pulmonary Edema.*—This was not found when the mean pulmonary arterial pressure was below 26 mm. Hg at rest. This was found in three of eighteen patients in the mild group, in none of the moderate group, and in five of twelve in the severe group.

OPERATIVE FINDINGS

Description of the mitral valve from autopsy or operation was obtained in twenty-two patients. Of seven patients in the mild group, three had severe mitral stenosis and four had moderate mitral stenosis. One had mitral insufficiency. Of six in the moderate group, five had severe mitral stenosis; one had moderate mitral stenosis; two had mitral insufficiency. Of nine in the severe group, seven had severe mitral stenosis. Mitral insufficiency was present in three; two had mitral insufficiency without severe mitral stenosis. These last patients had Grade 3 apical systolic murmurs and gross cardiac enlargement.

In general, more severe mitral stenosis was found in patients with higher pulmonary arterial pressures. However, the finding of severe pulmonary hypertension did not necessarily exclude predominant mitral insufficiency in the presence of marked cardiac enlargement and a loud apical systolic murmur. On the other hand, severe mitral stenosis was found with a resting mean pulmonary arterial pressure as low as 22 mm. Hg.

DISCUSSION

It was impossible to evaluate the right atrial systolic peak pressure as a guide to pulmonary hypertension from the data. Only eighteen observations were made; some high atrial pressures were seen in the low pulmonary pressure range; in the three observations associated with severe pulmonary hypertension, the right atrial "A" wave was within normal pressure limits. Auricular fibrillation was seen somewhat more often at higher pulmonary pressures but was seen so often at lower pressures that it was no help. This arrhythmia was observed when the pulmonary arterial pressure was as low as 18 mm. Hg.

The x-ray evidence of right ventricular hypertrophy was usually marked in the severe group. It was occasionally marked in the mild group, especially if rheumatic activity or damaged myocardium was present (Figs. 1-5). Fig. 1, patient J.V., demonstrates a relatively small heart, showing slight evidence of right ventricular enlargement in a patient with mitral stenosis and with a normal mean pulmonary arterial pressure of 15 mm. Hg. Figs. 2 and 3 demonstrate

relatively small hearts in association with severe pulmonary hypertension in patients with mitral stenosis and moderate evidence of right ventricular hypertrophy. Fig. 4 shows the cardiac x-ray of a patient (R.K.) with marked general and right ventricular enlargement in the presence of mild pulmonary hypertension (mean = 29 mm. Hg). Fig. 5 shows marked generalized and right ventricular enlargement in a patient (C.K.) with severe pulmonary hypertension (mean pressure = 78 mm. Hg). These figures exemplify the difficulty in predicting pulmonary blood pressure from the over-all size of the heart, or from

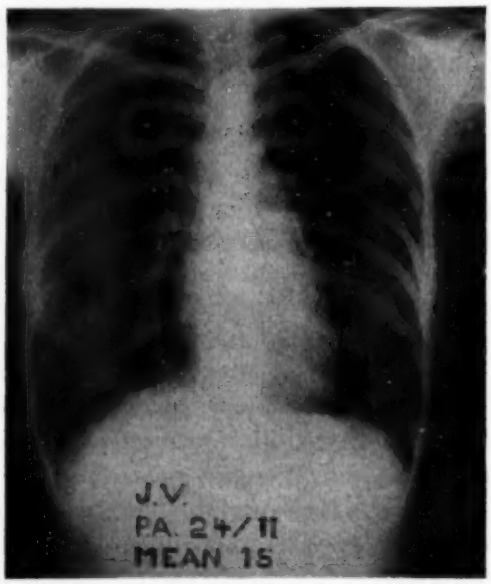

Fig. 1.—Chest teleroentgenogram of a 30-year-old woman with mitral stenosis and normal resting pulmonary arterial pressure, showing slight evidence of right ventricular enlargement and normal transverse cardiac diameter.

the size of the right ventricle as determined radiologically. However, the three patients having marked right ventricular hypertrophy with mild pulmonary hypertension had marked increase in the transverse diameter of the heart.

Evidence of right ventricular hypertrophy in the electrocardiogram, especially in precordial Lead V_1, was very helpful in suggesting fairly marked pulmonary hypertension. In only one instance, and then in the presence of active carditis, was even suggestive evidence of right ventricular hypertrophy seen with mean pressures below 28 mm. Hg. Consistent evidence of right ventricular hypertrophy was found when mean pulmonary arterial pressures were 42 mm. Hg or above, except in one patient who had electrocardiographic evidence of an old myocardial infarction. In general, precordial Lead V_1 seemed a more sensitive indicator of right ventricular hypertrophy than did the presence of right axis deviation or an abnormal axis deviation index. The value of the electrocardiogram in this respect has been stressed by others.[6]

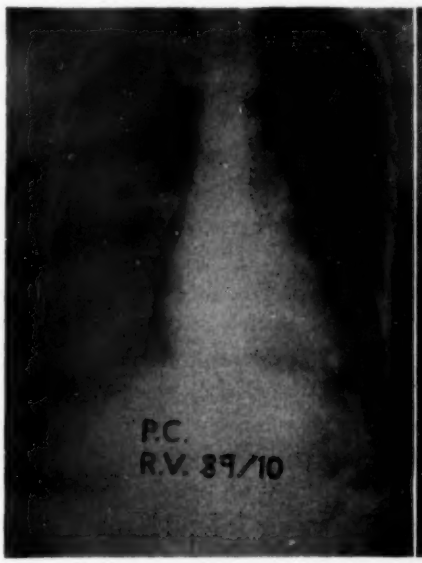

Fig. 2.

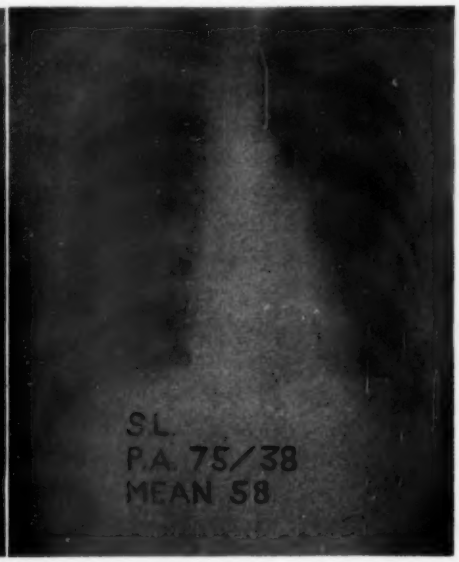

Fig. 3.

Fig. 2.—Chest teleroentgenogram of a 36-year-old woman with mitral stenosis and severe pulmonary hypertension, showing normal transverse cardiac diameter and moderate right ventricular enlargement.

Fig. 3.—Chest teleroentgenogram of a 37-year-old woman with mitral stenosis and severe pulmonary hypertension, showing normal transverse cardiac diameter and moderate right ventricular enlargement.

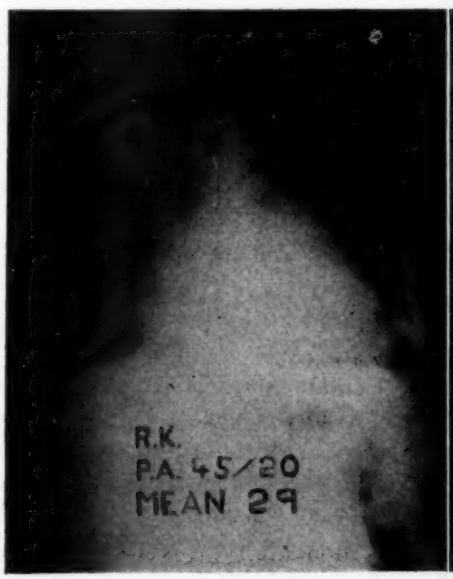

Fig. 4.

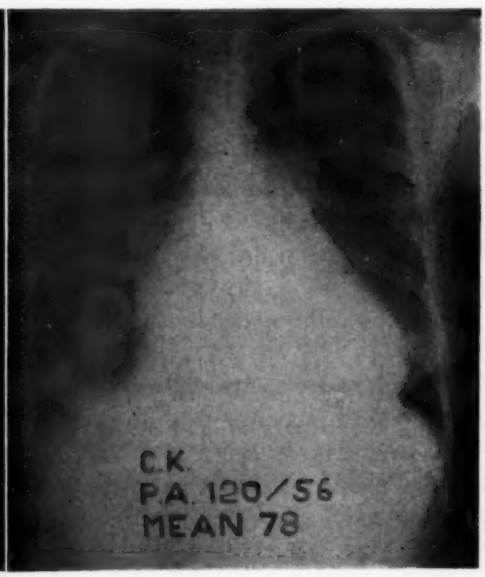

Fig. 5.

Fig. 4.—Chest teleroentgenogram of a 43-year-old woman with mitral stenosis and mild resting pulmonary hypertension, showing marked right ventricular and generalized cardiac enlargement.

Fig. 5.—Chest teleroentgenogram of a 41-year-old woman with mitral stenosis and severe pulmonary hypertension, showing marked right ventricular and generalized cardiac enlargement.

The intensity of the apical diastolic murmur or the presence of an apical diastolic thrill was of no help in suggesting marked pulmonary hypertension or tight mitral stenosis. If anything, loud murmurs and thrills were found more often in the mild group.

The intensity of the pulmonary second sound was of no help. When it was quite loud, the mean pulmonary arterial pressure was 29 mm. Hg or more; however, the pulmonary second sound was often only slightly or moderately accentuated in the severe group.

The presence of hemoptysis was most frequently observed in the severe group; however, it was often absent in this group and was on occasion present at relatively low pressures. This criterion was of little help as a guide to pulmonary hypertension.

Right ventricular failure, as indicated by peripheral edema, neck vein distention, and hepatomegaly, was found with increasing frequency as the pulmonary hypertension became more severe. It was found in all save one of the severe group. It was found in five of eighteen patients in the mild group, but not in association with mean pulmonary arterial pressures below 27 mm. Hg except in one patient (C.Q.) with active carditis.

Pulmonary edema was found rather infrequently in this study. It was found more often in the severe group but was found as low as 26 mm. Hg mean pulmonary arterial pressure. It was not a helpful guide to the level of pulmonary arterial pressure.

The findings in the "average" subject in this study with severe pulmonary hypertension in association with isolated mitral stenosis may be described as follows:

1. There is usually a history of right ventricular failure.
2. The electrocardiogram shows evidence or suggestive evidence of right ventricular hypertrophy in precordial Lead V_1.
3. The x-ray of the heart shows moderate or marked right ventricular hypertrophy, but the transverse diameter of the heart is often normal or only slightly above normal.
4. The apical diastolic murmur may be of any intensity but is more often soft than not.
5. The pulmonary second sound is accentuated but is usually only moderately so.

Left parasternal heave due to right ventricular enlargement was found in each of eight patients examined with severe hypertension in the pulmonary circulation. However, it was not marked in some with severe hypertension and was prominent in two patients with mean pulmonary arterial pressures of 29 mm. Hg and considerable cardiac dilatation. We agree with Whitaker[6] that this sign is usually found when severe pulmonary hypertension is present but is also found in association with relatively mild pulmonary hypertension, especially if the right ventricle is dilated.

SUMMARY

Forty patients having rheumatic heart disease and mitral stenosis were studied clinically and by cardiac venous catheterization in an attempt to develop

clinical criteria for the estimation of the degree of pulmonary hypertension. The patients were divided into three groups according to the mean pulmonary arterial blood pressure: mild or no pulmonary hypertension, below 30 mm. Hg; moderate pulmonary hypertension, 30 to 49 mm. Hg; severe pulmonary hypertension, above 50 mm. Hg. Eighteen subjects were in the mild group; ten were moderate; twelve were severe.

The following criteria were evaluated:

1. The height of the "A" wave of the right atrial pressure pulse. This was of no help in this group.

2. Roentgen evidence of right ventricular hypertrophy. This usually indicated rather severe pulmonary hypertension when marked, if the transverse diameter of the heart was not greatly increased.

3. Precordial Lead V_1 of the electrocardiogram was very helpful in evaluating the degree of pulmonary hypertension. In general, evidence of right ventricular hypertrophy was not found with mean pulmonary arterial pressures below 28 mm. Hg and was consistently present with mean pulmonary pressures of 42 mm. Hg or above.*

4. The intensity of the apical diastolic murmur was of no help in evaluating pulmonary hypertension. Intense apical murmurs and thrills were often associated with mild pulmonary hypertension and only moderate mitral stenosis.

5. The intensity of the pulmonic second sound was of no help. Severe pulmonary hypertension was often associated with only slight or moderate accentuation of the sound.

6. Hemoptysis was more frequent in severe pulmonary hypertension but was observed at all pressure levels.

7. Right heart failure was almost constant in the severe group. It was usually absent in the mild group unless associated with an increase in the transverse diameter of the heart.

8. Pulmonary edema was not seen with pulmonary arterial mean pressures below 26 mm. Hg but was often absent at higher pressure levels.

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*Since the writing of this paper, electrocardiographic evidence of right ventricular hypertrophy was found in one patient with mitral stenosis and a mean pulmonary arterial pressure of 21 mm. Hg; another patient with mitral stenosis had a mean pulmonary arterial pressure of 52 mm. Hg and no evidence of right ventricular hypertrophy in Lead V_1.

THE LIVER IN CONGESTIVE HEART FAILURE

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HEPATIC abnormalities constitute common and important secondary effects of congestive heart failure. Considerable information has been accumulated on the liver in heart failure, including anatomic changes,[1-10] biochemical alterations,[11-18] and physiologic disturbances.[19] The present report is based on histologic studies of the liver correlated with clinical and biochemical findings in seventy-five patients with congestive heart failure. The investigation was undertaken to further the evaluation of the mechanism and significance of hepatic abnormalities in chronic circulatory congestion.

MATERIALS AND METHODS

The selected patients with congestive heart failure were taken from routine hospital admissions. Each patient was on a regimen which included bed rest, sodium restriction, diuretics, and digitalis. Eighteen patients had relief of all clinical evidence of heart failure after treatment, twenty patients showed hepatomegaly despite disappearance of other evidence of congestive failure, and thirty-seven patients had persistent fluid retention. Ages of patients ranged from 30 to 79 years. Forty-five were men and there were thirty women. Thirty-three patients had rheumatic heart disease; twenty-three patients had hypertensive heart disease; twelve patients had arteriosclerotic heart disease; two patients had chronic cor pulmonale; two patients had constrictive pericarditis; two patients had thyroid heart disease; and one patient had syphilitic heart disease. Congestive heart failure had been present from six weeks to twelve years. Each patient had a functional capacity of Grade 3 or Grade 4 according to American Heart Association standards. Forty patients had auricular fibril-'ation, and thirty-five patients had normal sinus rhythm.

Biochemical liver function studies included serum bilirubin,[20] serum alkaline phosphatase,[21] Bromsulphalein excretion,[22] total serum cholesterol and cholesterol esters,[23] serum albumin and globulin,[24] cephalin-cholesterol flocculation,[25] thymol turbidity,[26] prothrombin time,[27] and glycogen storage capacity.[28] Serum bilirubin of more than 1.0 mg. per cent, retention of

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Bromsulphalein of 5 per cent or more, and a serum alkaline phosphatase greater than 5 Bodansky units were considered abnormal. Total cholesterol below 150 or above 240 mg. per cent with less than 50 to 70 per cent of the total being esterfied was classified as abnormal. Two-plus to four-plus cephalin flocculation in forty-eight hours, thymol turbidity of 5 units or more, and total serum protein of less than 6.8 grams per 100 c.c., or reversal of the albumin-globulin ratio were considered abnormal. Normal prothrombin time was within one second of the control values, and normal glycogen storage consisted of a rise in blood sugar of 40 mg. per cent or more within one hour after administration of epinephrine.

Liver biopsy was performed with the Vim Silverman needle without complications.[29] Thirty-eight patients had serial aspiration biopsies. Ten patients had post-mortem studies. The presence of passive congestion, central necrosis, and/or centrilobular fibrosis was interpreted as stages of the classical lesions attributed to congestive failure.[30-33] Additional diagnoses included diffuse fibrosis, focal inflammation, and fatty liver.

A histologic diagnosis of passive congestion was made on the basis of dilated central veins and sinusoids which contained red blood cells in varying numbers (Fig. 1,*A*). A diagnosis of centrilobular fibrosis was based on the presence of thickening of the central vein with or without fibrosis extending toward the portal area (Fig. 1,*B*). Central necrosis was diagnosed by congestion of the central vein and absence of liver cells in the centrilobular area (Fig. 1,*C*). A diagnosis of fatty liver was made when intracellular or extracellular fat globules occupied more than 10 per cent of the biopsy section (Fig. 1,*D*). A diagnosis of diffuse fibrosis was made on the basis of fibrous connective tissue in the non-acinar area of the hepatic lobule, bile duct proliferation, and pseudolobulation with or without fatty metamorphosis and lymphocytic infiltration (Fig. 1,*E*). The diagnosis of focal infiltration was based on the presence of small intralobular foci of lymphocytes or polymorphonuclear leukocytes not in relation to the central vein or portal areas (Fig. 1,*F*).

OBSERVATIONS

Seventy-one (95 per cent) patients had hepatomegaly; thirty-seven (49 per cent) patients had ascites; sixteen (21 per cent) patients had jaundice; nine (12 per cent) patients had splenomegaly; and eight (11 per cent) patients had hepatic pain. The incidence of clinical abnormalities was proportionately the same in the sexes. Neither type of heart disease nor duration of heart failure could be correlated with signs and symptoms. On the other hand, the occurrence of jaundice and hepatic pain was related to the acuity and severity of failure. Each of the patients with jaundice had Grade 4 heart failure. Hepatic pain occurred in patients with acute onset of failure or an exacerbation of chronic failure.

Liver function studies revealed biochemical changes in each of the seventy-five patients. Serum protein alterations were uniformly present. Decreased glycogen storage was present in 93 per cent of the patients, prothrombin deficiency in 90 per cent, abnormal Bromsulphalein retention in 78 per cent, and

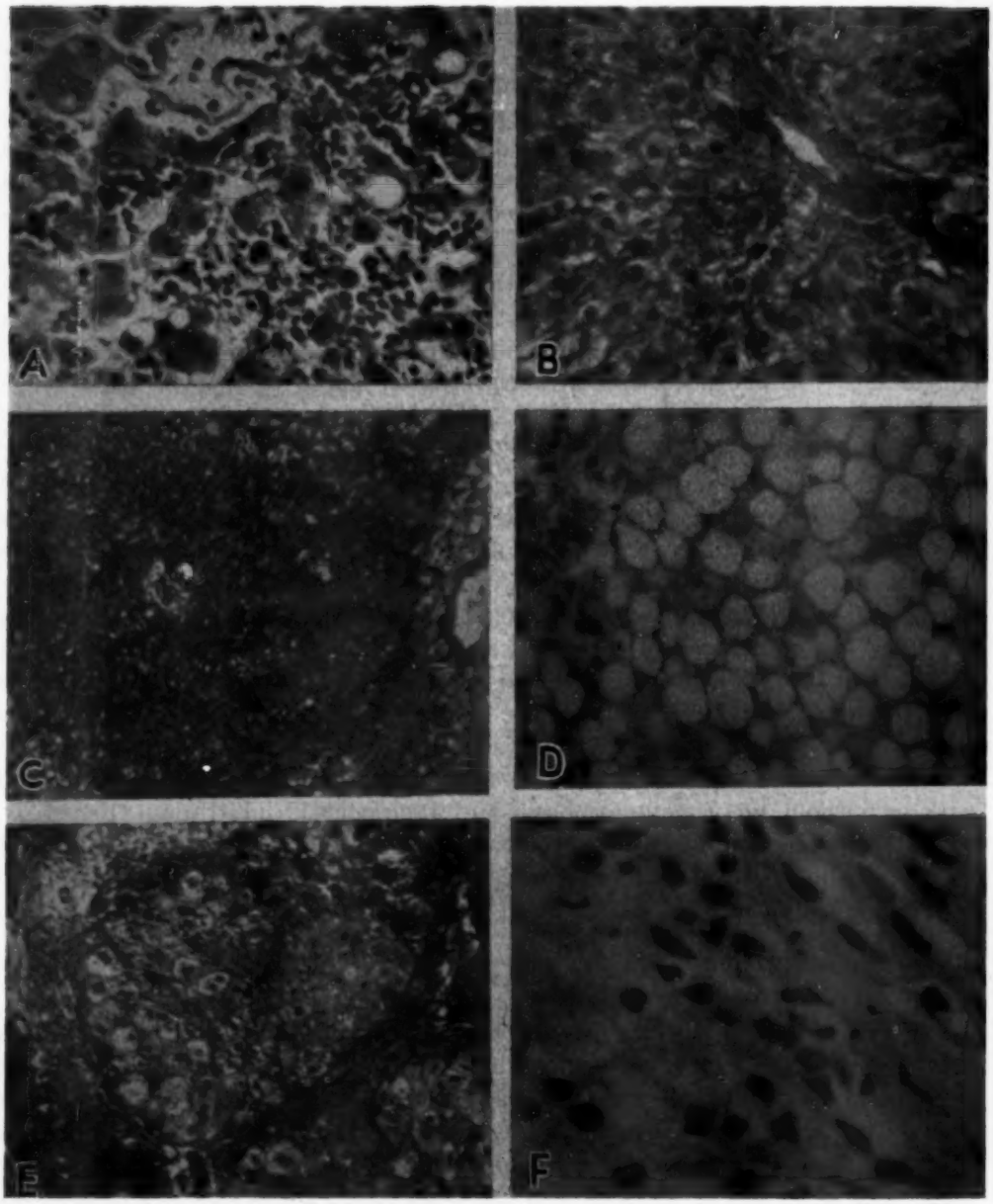

Fig. 1.—Histologic findings in congestive heart failure: *A*, Passive congestion with normal central vein (Case 1); *B*, Passive congestion with centrilobular fibrosis one year later (Case 1); *C*, Passive congestion with central necrosis; *D*, Fatty liver (Case 2); *E*, Portal cirrhosis showing pseudolobulation and periportal fibrosis four years later (Case 2); *F*, Focal infiltration.

hyperbilirubinemia in 40 per cent. A positive cephalin flocculation was present in 37 per cent of the patients, hyperglobulinemia in 34 per cent, cholesterol ester dissociation in 21 per cent, elevated alkaline phosphatase in 17 per cent, and a positive thymol turbidity in 11 per cent (Table I). Sex, age, type of heart disease, duration of heart failure, and severity of heart failure had no consistent influence on hepatic dysfunction. Prolonged, severe heart failure was associated with the most marked degrees of biochemical changes.

Needle biopsy of the liver showed normal liver or passive congestion in forty-seven (63 per cent) patients, central necrosis with congestion in seven (9 per cent) patients, centrilobular fibrosis with congestion in nine (12 per cent) patients, diffuse fibrosis in nine (12 per cent) patients, fatty metamorphosis in two (2.5 per cent) patients, and focal inflammation in one (1.5 per cent) patient. Histologic alterations could not be related to the type of heart disease, heart size, electrocardiographic findings, or presence of arrhythmia. The severity of heart failure and previous dietary habits were important determinants of anatomic changes. Severe heart failure was accompanied by central necrosis and exudation in the space of Disse. Recurrent episodes of failure led to centrilobular fibrosis in a patient followed over a four-year period (Fig. 1,*A* and *B*). Fatty liver and diffuse fibrosis occurred in patients whose previous diet was grossly deficient in protein. Alcoholism was the chief cause of dietary inadequacy in these patients. Serial biopsy showed the transition of fatty liver to diffuse fibrosis in two patients (Fig. 1,*C* and *D*).

CORRELATION OF HISTOLOGY WITH CLINICAL AND BIOCHEMICAL ABNORMALITIES

Clinical abnormalities could frequently be related to histologic changes. Ascites was most prominent in patients with centrilobular fibrosis and diffuse fibrosis on biopsy. Jaundice could be ascribed to hepatocellular changes alone in eleven (69 per cent) patients, and a combination of liver cell dysfunction and pulmonary infarction in five (31 per cent) patients. Biopsies showed passive congestion in ten patients, central necrosis in three patients, and diffuse fibrosis in three patients. Patients with central necrosis had the most intense icterus. The relationship of splenomegaly to hepatic changes was difficult to determine.

Biochemical studies could not be correlated with observed histology. Patients with normal histology had functional patterns which closely resembled those of patients with centrilobular fibrosis and diffuse fibrosis. Serial study of patients with progressive changes in morphology showed a concomitant deterioration in biochemical functional capacity.

THERAPEUTIC ASPECTS

It was not possible to predict therapeutic response from hepatic studies. Each of the patients with complete disappearance of signs of heart failure had

TABLE I. CORRELATION OF HISTOLOGY WITH BIOCHEMICAL FUNCTIONS AND CLINICAL FINDINGS IN CONGESTIVE HEART FAILURE

HISTOLOGIC DIAGNOSIS	EXCRETORY FUNCTION ABNORMALITIES IMPAIRED				METABOLIC FUNCTION ABNORMALITIES IMPAIRED				CLINICAL CHANGES			
	B.S.P. (%)	SERUM BIL. (%)	ALK. PHOS. (%)	CHOLESTEROL (%)	PROTEIN PARTITION (%)	CEPH. FLOCC. (%)	TYM. TURB. (%)	CHOLESTEROL PARTITION (%)	JAUNDICE (%)	ASCITES (%)	HEPATOMEGALY (%)	SPLENOMEGALY (%)
Passive congestion	83	26	6.3	21	100	35	9	2	4.2	25	100	8.5
Central necrosis	100	100	42	21	100	84	21	42	100	100	100	14.2
Centrilobular fibrosis	11	44	33	44	100	44	11	22	11	100	55	11
Focal inflammation	0	0	100	100	100	0	0	0	0	0	100	0
Diffuse fibrosis	100	66	22	11	100	33	11	33	44	100	66	33
Fatty liver	100	50	0	50	100	0	0	0	0	0	50	0

passive congestion on biopsy. Hepatic changes were rapidly altered with improvement in heart failure in twenty patients. The Bromsulphalein test, glycogen storage, prothrombin time, and cholesterol esters improved with cardiac compensation. Abnormalities of serum proteins, cephalin flocculation, thymol turbidity, and alkaline phosphatase often persisted after compensation.

Patients with fibrosis had persistent hepatomegaly or fluid retention refractory to treatment. Survival was related to the severity of hepatic disease in patients with necrosis or diffuse fibrosis on biopsy, and to the type of heart disease and severity of congestive failure in the others. Three patients with central necrosis died in heart failure; hematemesis and hepatic coma were responsible for death in four patients with diffuse fibrosis. Prognosis was poorest in patients with clinical jaundice, hypoalbuminemia, and central necrosis.

Refractoriness to cardiotherapy occurred in twenty patients with passive congestion, three patients with central necrosis, seven patients with central fibrosis, and seven patients with diffuse fibrosis. Refractoriness was attributed to hepatic abnormalities in fourteen (38 per cent) patients with diffuse fibrosis, four patients with central fibrosis, two patients with passive congestion and one patient with central necrosis. Hypoalbuminemia was an important factor in seven of these patients.

COMMENT

A study of the liver in congestive heart failure improves prognostic and therapeutic perspective. Use of a composite approach including clinical, biochemical, and histologic study is desirable in patients with hepatomegaly or fluid accumulation resistant to treatment. The hepatic lesion is as important as the cardiac dysfunction in patients with diffuse fibrosis of the liver. Careful attention to replacement and supportive therapy is necessary to forestall complications of liver disease.

Serial biopsy of a large number of patients with heart failure is necessary to determine the usual mechanism responsible for diffuse fibrosis of the liver in heart failure. It has been shown that central fibrosis which appears to begin under the stimulus of anoxia may progress to involve the entire liver.[30] This study supports this thesis but demonstrates that poor nutrition with a fatty liver may also be the precursor of the diffuse fibrosis encountered in heart failure. Provision of an adequate diet and early recognition and treatment of fatty liver are essential for prophylaxis.

A problem outside the scope of this paper is concerned with the influence of liver injury on normal cardiac dynamics. Clinical study occasionally reveals the onset of heart failure with progression of hepatic insufficiency. Kowalski and Abelmann have demonstrated an increased cardiac output in one-third of the patients with cirrhosis of the liver.[15] This becomes a practical problem when one considers the possibility of concomitant hepatic and cardiac injury with nutritional deficiency.

The association of fluid retention and primary liver disease suggests that alteration of hepatic function during heart failure may contribute to chronic circulatory congestion. The excretion of antidiuretic substance in liver disease

and heart failure has been extensively studied;[34] however, its role in congestive heart failure is not completely understood. Disturbance of a common regulating mechanism which controls renal tubular activity is probably responsible for fluid retention in both liver and heart disease. Hepatic vein hypertension, hypoalbuminemia, and decreased renal blood flow may represent critical factors which provoke fluid retention. Further study is desirable to determine specific relationships of anatomic, physiologic, and biochemical changes to fluid accumulation.

SUMMARY AND CONCLUSIONS

1. Biochemical liver function tests and needle biopsies of the liver were performed on seventy-five patients with congestive heart failure and correlated with clinical features. A composite of clinical, biochemical, and histologic study was helpful in patients with hepatomegaly or fluid accumulation resistant to treatment.

2. Serial biopsy studies demonstrated two mechanisms leading to liver fibrosis in heart failure: (a) passive congestion led to central necrosis and centrilobular fibrosis; (b) poor nutrition caused fatty liver and eventually diffuse fibrosis.

3. Survival periods were related to the severity of hepatic changes in patients with fibrosis or necrosis, and to the type of heart disease and the degree of heart failure in the others. Icterus, hypoalbuminemia, and diffuse fibrosis were often accompanied by fluid retention refractory to therapy. The prognosis in these cases was poor.

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INCREASED URINARY COPROPORPHYRINS FOLLOWING ACUTE MYOCARDIAL INFARCTION AND PULMONARY EMBOLISM

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AN increased secretion of porphyrins in the urine has been found not only in porphyrias proper but also in association with numerous other diseases. Among such disease conditions are reported various anemias, leukemias, hepatic lesions of various kinds and heavy metal poisonings (Watson[1]). In congestive heart failure, also, urinary porphyrins may be increased (Kämmerer[2] and Kaunitz[3]). Except in cases of porphyrias proper, the porphyrins secreted into the urine are usually of the coproporphyrin type.

Since we have been able to find in the literature available to us no reference to increased urinary coproporphyrins in association with myocardial infarction or pulmonary embolism, the observations made by us may be of interest.

CLINICAL MATERIAL AND METHODS

Our series comprises twelve healthy test subjects, twelve typical cases of myocardial infarction confirmed by the appearance of the classical pattern of injury and necrosis in the electrocardiogram, and five clinically typical cases of pulmonary embolism.

The urines were extracted with ether/glacial acetic acid (20:1) and the coproporphyrins were extracted from the ethereal extracts with equal portions of 0.1N hydrochloric acid until no fluorescence could be observed in the HCl phase when examined in ultraviolet light. The coproporphyrin chromogen was converted to porphyrin with 3N hydrochloric acid according to Eriksen.[4] The amount of coproporphyrin was determined according to Rimington and Sveinsson.[5] The results are stated in μg/24 hr.

RESULTS AND COMMENTS

The daily amounts of urinary coproporphyrins in healthy control persons are shown in Table I. The total coproporphyrins in these persons varied from 21 to 142 μg/24 hr. It is observed that the daily amounts of urinary coproporphyrins are somewhat lower than those reported by Zieve and associates[6] for

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normal values obtained by another method of determination. Since a porphyrin-free diet was found to have no noteworthy effect on the daily urinary coproporphyrin secretion of healthy subjects, as is evident also from earlier studies (Kaunitz[3]), it was not considered necessary to keep the test patients with acute myocardial infarction or pulmonary embolism on a porphyrin-free diet. In the cases of acute myocardial infarction an increased urinary coproporphyrin secretion was observed during the first two or three days following infarction. Table II shows the values obtained in these cases. The total urinary coproporphyrin varied during the first two or three days between 310 and 207 μg/24 hr. During the second and third weeks after infarction no elevated values were seen in the urinary coproporphyrin secretion.

TABLE I. URINARY COPROPORPHYRIN (μG/24 HR.) IN HEALTHY PERSONS

CASE NO.	SEX	AGE (YR.)	TOTAL COPROPORPHYRIN
1	M	55	110
2	M	50	113
3	F	49	21
4	F	22	25
5	M	46	35
6	F	20	50
7	M	31	65
8	M	35	97
9	M	38	142
10	M	27	49
11	M	60	95
12	F	27	39

Increased urinary coproporphyrins were also seen in association with acute pulmonary embolism during the first two or three days following occurrence of the embolism. During the second week this was no longer observable. The results for these patients are shown in Table III.

It is rather difficult to account for the increased urinary coproporphyrins in association with myocardial infarction and pulmonary embolism. They probably cannot be ascribed to an increased erythropoiesis, for no increase was seen in the number of reticulocytes. It also is hardly possible to consider it a result of cardiac insufficiency, for this condition was clinically established in one of our cases only (Case 6), in which the urinary coproporphyrins were no higher than in other cases of infarction.

An increased secretion of porphyrins in the urine has been reported in diseases of the liver (Watson and associates).[7] Centrilobular hepatic necrosis has been frequently seen in association with a fatal myocardial infarction and it has been ascribed chiefly to shock (Clarke).[8] In our cases this explanation of the elevated urinary coproporphyrin values does not seem to apply, since a definite shock was clinically diagnosed in one case only (Case 8). Four patients with infarction (Cases 6 to 9) and two with pulmonary embolism (Cases 5 to 6) were given a number of liver function tests (bromsulfophthalein, galactose, hippuric acid, and Takata tests), but no changes could be demonstrated.

TABLE II. URINARY COPROPORPHYRIN (μG/24 HR.) IN CASES OF ACUTE MYOCARDIAL INFARCTION

CASE NO.	SEX	AGE (YR.)	DAYS SINCE INFARCTION	TOTAL COPRO-PORPHYRIN	RETICULOCYTES (%)
1	M	54	2	207	0.3
			14	74	0.4
2	F	63	3	303	0.1
			14	50	0.3
3	M	62	3	283	0.4
			14	32	0.4
4	M	54	3	232	0.6
			15	28	0.4
5	M	46	2	310	0.5
			10	34	0.3
6	M	64	2	260	0.6
7	M	49	2	293	0.4
			12	48	0.4
8	F	49	3	240	0.6
			10	57	0.5
9	M	51	2	236	0.5
			8	32	0.6
10	M	67	3	223	
			6	180	
			11	125	
11	M	42	1	75	
			6	210	
			8	226	
			16	129	
			27	42	
12	M	70	2	298	
			6	185	
			10	56	

TABLE III. URINARY COPROPORPHYRIN (μG/24 HR.) IN CASES OF ACUTE PULMONARY EMBOLISM

CASE NO.	SEX	AGE (YR.)	DAYS SINCE EMBOLISM	TOTAL COPRO-PORPHYRIN
1	F	36	2	203
			8	40
2	M	28	2	262
			10	34
3	F	30	3	266
			10	44
4	F	42	3	287
			8	69
5	M	54	2	266
			7	98

It is interesting to note that Evans, Wood and Brew[9] have found increased urinary urobilinogens following both myocardial infarction and pulmonary embolism. They were not able to demonstrate that this increased secretion was due to shock or to cardiac insufficiency. No changes were found in their series in the liver function tests (bromsulfophthalein, cephalin flocculation, and thymol turbidity tests). They were of the opinion that the increased urobilinogen secretion was due in their cases to the effect of stress on the function of the liver.

SUMMARY

The authors have studied the secretion of coproporphyrins in the urine in twelve cases of myocardial infarction, five cases of pulmonary embolism and twelve healthy persons. In the healthy subjects the daily amount of urinary coproporphyrins was 21 to 142 μg. During the first two or three days following myocardial infarction and pulmonary embolism an increase occurred in the daily urinary coproporphyrin secretion, the total amount being 310 to 207 μg/24 hr. in the patients with infarction and 287 to 203 μg/24 hr. in patients with pulmonary embolism.

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DECHOLESTEROLIZING AGENTS

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CHEMICAL and physical abnormalities of lipid materials in the plasma have been linked to the pathogenesis of atherosclerosis. Qualitative or quantitative changes in serum lipids initiate their deposition in susceptible arterial sites. The conclusion that hypercholesteremia is harmful and its lowering desirable encouraged the evaluation of many therapeutic agents and procedures presumed in some manner to accomplish this. These include the use of long-chained unsaturated fatty acids,[1] brain extract,[2] plant sterols including sitosterol,[3] eggplant,[4] and artichokes.[5] Thyroid[6] has been used to increase cholesterol catabolism. A polysorbate 80-choline-inositol complex is presumed to make the cholesterol molecule more easily filterable through the renal glomerules and more accessible to the adrenal cortex for its requirements.[7]

Unequivocable evidence of reduction of blood cholesterol has been achieved only with marked restriction of dietary fat.[8] Observation of prolonged periods of fat restriction indicates a return of cholesterol to prerestriction levels.[9]

The following experimental procedures included repeated serum cholesterol determinations in control cases and in subjects treated with the previously mentioned decholesterolizing agents. No effect on serum cholesterol that could be directly attributed to the agent used was noted.

MATERIALS AND METHODS

For control purposes serum cholesterol levels were determined at 7 to 10 day intervals in eighteen subjects.

Sitosterol, a nonabsorbable sterol, which presumably draws cholesterol from the gastrointestinal tract, was prepared in a fairly palatable liquid form.* Seven grams were fed daily in divided doses for 6 weeks to twenty-five subjects, and serial cholesterol determinations were done. This therapeutic regimen was preceded by three control observations over a 4-week period.

Chophytol,* a special preparation of Jerusalem artichoke, which is available in France, was given to thirteen subjects similarly observed.

Polysorbate 80-choline-inositol complex was given for 6-week periods to twelve subjects similarly observed.

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*Sitosterol and Chophytol were kindly supplied by Raymond C. Pogge, M.D., Director of the Department of Medical Research, the William S. Merrell Co., Cincinnati, Ohio.

Smaller groups were treated with eggplant,* Tween 80,† pancreatin concentrate,‡ Resion, and Vitamin E.†

Total serum cholesterol was determined by a modification of the Sperry-Schoenheimer method.[10]

RESULTS

Individual Fluctuation of Serum Cholesterol Levels.—Table I demonstrates serum cholesterol determinations in the same individuals when observed at 7 to 10 day intervals for prolonged periods. Individuals vary in the relative stability of their serum cholesterol levels. In some subjects determinations were consistently within a narrow range while others demonstrated wide fluctuations, the more extreme fluctuations occurring in those with higher serum levels. The differences noted serve to emphasize the need for great caution in interpreting as significant, changes during therapy considered specific.

TABLE I. INTERVAL DETERMINATION OF TOTAL SERUM CHOLESTEROL IN UNTREATED SUBJECTS

Mg. %

	WEEKS													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
S.N.	437	390	311	410	290	287	332	277	315					
S.F.	330	324	315	345	325	327	295	322	318					
B.B.	291	313	299	307	265	308	308	308	300	294	304	302		
F.K.	173	272	249	204										
F.L.	1276	1515	359	625	598	591	481	428	370	284	329	289	342	313
S.L.	436	459	750	531	443	502	384	285	465					
J.P.	399	430	411	465	589	527	457							
R.R.	288	250	270	325	281	289	264	307	333	320				
A.R.	205	315	267	289	347									
L.L.	395	349	362											
P.C.	329	289	283											
C.O.	292	216	264	185	232	202	207	232	229	225	213	227		
A.H.	197	242	200											
N.I.	216	213	246											
S.H.	236	244	238	240	245	238								
F.R.	411	409	394	402	419	412	409							
S.T.	288	286	294	287	268	282	286	289						
F.P.	298	306	304	286	294	302								

Sitosterol.—Table II indicates that no marked alteration in serum cholesterol levels was achieved by feeding 7 Gm. of sitosterol daily. There is no indication that this therapeutic device is effective in lowering serum cholesterol levels.

Chophytol.—Thirteen patients similarly observed before and during therapy with Chophytol evidenced no great change in total serum cholesterol levels (Table III). Under the conditions here followed, Chophytol appeared to have no effect on serum cholesterol.

*The eggplant preparation was supplied in tablet form by Harvey L. Daiell, M.D., Director Scientific Department, Lakeside Laboratories Inc., Milwaukee, Wis.

†Tween 80 and Vitamin E were supplied by Dr. Louis Freedman, Research Director of the U. S. Vitamin Corporation, New York, N. Y.

‡Pancreatin concentrate was supplied by David Klein, Ph.D., The Wilson Laboratories, Chicago Ill.

TABLE II. INTERVAL DETERMINATION OF TOTAL SERUM CHOLESTEROL IN SUBJECTS TREATED WITH 7 GM. SITOSTEROL DAILY

CASE NO.	CONTROL PERIOD			WEEK OF THERAPY		
	0	2 WK.	4 WK.	2 WK.	4 WK.	6 WK.
1	210	227	221	248	216	231
2	214	204	217	198	211	207
3	220	231	225	205	189	193
4	230	244	234	207	197	220
5	265	272	248	240	245	252
6	723	680	663	690	925	850
7	164	172	158	143	150	149
8	256	270	262	259	235	232
9	260	246	253	250	238	230
10	420	409	372	386	380	341
11	308	304	312	268	302	274
12	225	232	213	217	211	238
13	250	222	241	228	205	219
14	411	328	350	321	345	329
15	416	384	371	392	420	443
16	236	261	265	238	237	245
17	186	174	171	175	156	161
18	379	362	368	325	338	333
19	204	249	228	219	216	200
20	272	270	277	258	258	251
21	298	274	304	246	265	251
22	231	242	226	227	240	234
23	233	247	228	214	219	226
24	346	365	331	337	349	327
25	325	291	295	279	311	300
Mean	291.28	286.16	281.32	270.80	282.32	277.44
Standard error of mean	23.12	16.74	19.86	21.18	30.08	27.04

TABLE III. INTERVAL DETERMINATION OF TOTAL SERUM CHOLESTEROL IN SUBJECTS TREATED WITH CHOPHYTOL (JERUSALEM ARTICHOKE)

CASE NO.	*Mg. %*					
	CONTROL PERIOD (WEEKS)			INTERVALS DURING THERAPY (WEEKS)		
1	274	285	275	261	275	270
2	252	259	270	237	250	259
3	299	311	310	294	292	305
4	270	268	247	284	276	279
5	310	312	308	285	292	296
6	230	256	244	249	246	251
7	262	258	264	254	262	255
8	260	230	217	253	245	266
9	234	247	270	227	235	252
10	356	370	359	346	348	360
11	284	264	292	278	286	292
12	212	232	218	206	238	220
13	186	208	194	208	212	202

Polysorbate 80-Choline-inositol Complex.—A similar study conducted using polysorbate 80-choline-inositol complex in twelve subjects revealed no significant change in total serum cholesterol concentration. The therapy did not appear to affect cholesterol levels in these twelve subjects under the conditions of the present experiment (Table IV).

TABLE IV. INTERVAL DETERMINATION OF TOTAL SERUM CHOLESTEROL IN SUBJECTS TREATED WITH POLYSORBATE 80-CHOLINE-INOSITOL COMPLEX

CASE NO.	*Mg. %*					
	CONTROL PERIOD (WEEKS)			INTERVALS DURING THERAPY (WEEKS)		
1	284	282	272	278	268	274
2	310	294	298	286	284	273
3	224	252	246	220	234	238
4	287	274	270	263	256	266
5	212	244	238	227	234	213
6	345	338	344	344	346	339
7	372	354	357	322	326	339
8	314	298	310	307	302	314
9	206	211	216	210	217	211
10	254	252	258	245	256	256
11	269	284	274	275	274	270
12	288	299	292	263	271	274

Other Therapeutic Preparations.—No changes were observed in serum cholesterol levels in subjects treated with eggplant, Tween 80, pancreatin concentrate, Resion, or Vitamin E.

DISCUSSION

The preceding observations indicate a wide range of serum cholesterol levels in some individuals and a lack of response to various therapeutic agents. An approximate individual level of cholesteremia exists, and this is altered at times by temporary stressful conditions and low-fat diets, either self-imposed or determined by gastrointestinal changes. The range of this approximate level is quite wide in some individuals, usually in those with hypercholesteremia. This may be explained by repeated stressful conditions, and some adaptive reaction which appears to return serum cholesterol to control levels. Mann and White[11] have demonstrated that the physiologic response to stress is a reduction of total serum cholesterol.

Cholesterol is an essential constituent of all body fluids and cells, especially those of the brain. It is constantly synthesized, destroyed, and excreted under normal conditions. Hypercholesteremia indicates increased plasma saturation but has no relationship to tissue availability or utilization. Hypercholesteremia may possibly be a protective mechanism to insure proper tissue utilization when the mechanism of cholesterol metabolism is impaired.

Clinical manifestations have been noted in patients subjected to extreme fat restriction for long periods.[13] Perhaps it is well that a homeostatic mechanism

prevents a prolonged reduction of serum cholesterol levels. Intrinsic change in the cholesterol-binding properties of the plasma protein causes a reduction in the rate of destruction of cholesterol in the liver[12] and so may elevate cholesterol levels. Hypercholesteremia is indirectly related to liver function.[12] Therapy should be directed to improvement of liver function and, through this, improved metabolism of cholesterol. Gross attempts to lower serum cholesterol levels artificially may be unphysiologic.

CONCLUSIONS AND SUMMARY

On the basis of our presently reported findings, it is impossible to assign, to any therapeutic agent investigated, the ability to lower serum cholesterol levels. It would appear that previously presented alterations in serum cholesterol levels following administration of these agents were related either to unrecognized stressful situations or self-imposed fat restriction.

The concept of the value of altering serum cholesterol levels for therapeutic purposes is a questionable one. It is rather suggested that hypercholesteremia is a manifestation of fat metabolism dysfunction which is indirectly related to liver function. Therapeutic efforts should be directed rather to the liver dysfunction represented by and the cause of the hypercholesteremia, than to hypercholesteremia itself.

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PERSISTENT LEFT SUPERIOR VENA CAVA

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WHILE bilateral superior venae cavae occur normally in reptiles, birds, and a few mammals, the persistence of the left superior vena cava is unusual in man. In 1946, Sanders[1] reported one case of persistent left superior vena cava and was able to find 205 additional cases in the literature. All of these cases had been discovered at necropsy with the apparent incidence of the condition being approximately 1:350 cadavers. The first cases to be recognized in vivo were reported by Castellanos and associates[2] who diagnosed the presence of a persistent left superior vena cava from angiocardiograms. Additional cases have since been recognized on angiocardiograms, during cardiac catheterization and during intrathoracic operations.[3-10]

Since a persistent left superior vena cava is often of more than academic interest, we are reporting three additional cases, all of which were recognized during cardiac catheterization studies.

CASE REPORTS

CASE 1. The patient was a 22-year-old woman who had experienced mild exertional dyspnea since childhood. She had never had cyanosis, edema, or hemoptysis.

Physical examination revealed a loud systolic murmur and thrill, of maximal intensity at the left sternal border in the third intercostal space. The second heart sound at the pulmonic area was of increased intensity and was followed by a short, early diastolic murmur. No clubbing, cyanosis, or edema was present, and the physical examination of the lungs was normal. An incomplete right bundle branch block was present in the electrocardiogram. Fluoroscopy demonstrated the presence of mild right ventricular enlargement and expansile hilar artery pulsations. Cardiac catheterization was performed via the left median basilic vein on July 15, 1953, and via the right median basilic vein on July 29, 1953. The data obtained are shown in Table I. When introduced from the left arm, the catheter passed downward behind the left portion of the heart shadow and then curved to the right to enter the right atrium. The catheter then passed up the right superior vena cava into the right jugular vein (Fig. 1.) Although the catheter could be maneuvered into the right ventricle (Fig. 2), the pulmonary artery was not entered. When the procedure was repeated from the right side, the catheter was readily passed to the pulmonary artery, as well as through the coronary sinus to the left superior vena cava. An angiocardiogram which was performed at a later date from the right side failed to show any communication between the superior venae cavae. Reopacification of the right atrium and ventricle was clearly demonstrated. From the data obtained, it was concluded that the patient had bilateral superior venae cavae with the left superior vena cava draining to the right atrium through the coronary sinus.

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An atrial septal defect was considered likely because of the marked rise in oxygen saturation of the blood in the right atrium. In addition, the possibility of anomalous pulmonary venous drainage into the left superior vena cava was strongly considered because of the elevated oxygen saturation of the blood in this vessel.

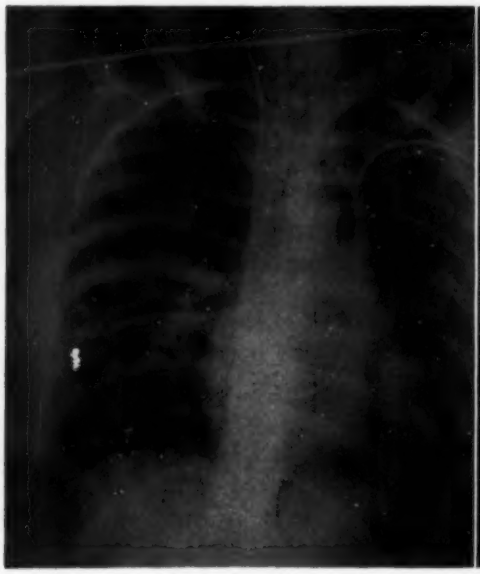

Fig. 1.

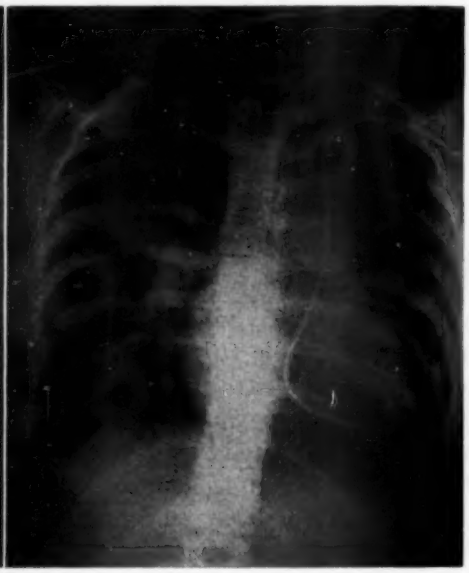

Fig. 2.

Fig. 1.—Case 1. The cardiac catheter may be seen passing down a persistent left superior vena cava to enter the right atrium via the coronary sinus. The tip of the catheter has passed up the right superior vena cava to the right jugular vein.

Fig. 2.—Case 1. The tip of the catheter lies in the right ventricle after passing through the left superior vena cava, coronary sinus, and right atrium.

TABLE I. DATA OBTAINED DURING CARDIAC CATHETERIZATION FROM THE LEFT (7/15/53) AND RIGHT (7/29/53) ARMS IN CASE I

SITE	OXYGEN SATURATION* (%)		PRESSURE (MM. HG)	
	7/15/53	7/29/53	7/15/53	7/29/53
Left superior vena cava				
(a) Near left subclavian vein	71–72	79	Mean = 10	—
(b) Middle third	81–83	85	—	—
(c) Close to right atrium	—	91	—	—
Right atrium				
(a) Near coronary sinus	82	—	—	—
(b) Mid-	91–93	94	—	—
Right superior vena cava	69	76	—	—
Right ventricle	88–90	95	36/0	35/0
Right pulmonary artery	—	90	—	32/14
Left pulmonary artery	—	94	—	32/14
Main pulmonary artery	—	90–93	—	36/12
Inferior vena cava	81	83		
Brachial artery	99.5	99.5	—	116/70

*Oxygen saturations were determined with a cuvette oximeter.[11]

CASE 2. A 36-year-old white woman had no symptoms until one year previously when she developed mild shortness of breath on exertion, easy fatigability, and a vague pressure sensation substernally. Orthopnea, paroxysmal dyspnea, cyanosis, and hemoptysis had never occurred.

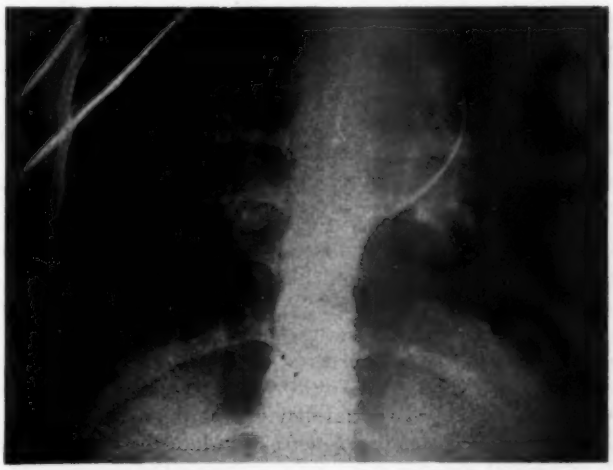

Fig. 3.—Case 2. The catheter tip lies in the pulmonary artery after having passed through the left superior vena cava, right atrium, and right ventricle (verified by pressure curves).

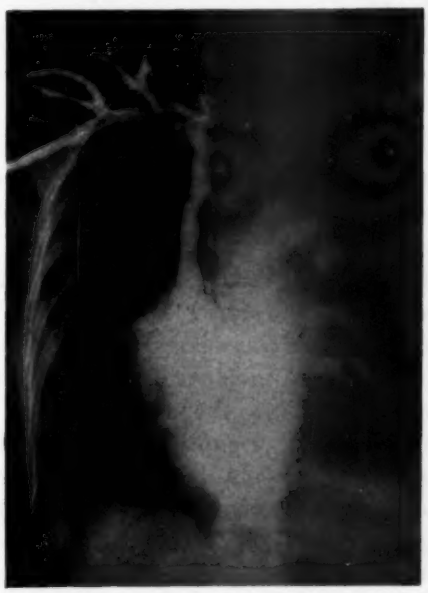

Fig. 4.—Case 2. The presence of a right superior vena cava is evident on the angiocardiogram. No anastamosis is evident between the two superior venae cavae.

On examination, there was no clubbing, cyanosis, or edema and the lungs were normal. A moderately loud systolic murmur was best heard in the second and third left intercostal spaces, parasternally. No thrills or diastolic murmurs were present. The second pulmonic sound was split but of normal intensity. The electrocardiogram showed a complete right bundle branch block and broad notched P waves in Leads I and II. Fluoroscopy revealed enlargement of the right ventricle and right atrium, increased vascular markings in the lungs, and expansile hilar artery pulsations.

Cardiac catheterization by way of the left median basilic vein was performed on Jan. 27, 1954. The catheter passed from the left subclavian vein downward along the left border of the heart via an anomalous left superior vena cava to enter the right atrium through the coronary sinus (Fig. 3). The catheter readily passed from the right atrium to the right ventricle and pulmonary artery. The pressures obtained from the various chambers were normal. There was a marked rise in the oxygen saturation of the blood samples obtained from the right atrium (82 to 85 per cent) as compared to those obtained along the course of the left superior vena cava (52 to 58 per cent). The brachial artery blood had a saturation of 94.5 per cent. These data indicate the presence of an atrial septal defect or anomalous pulmonary venous drainage to the right atrium or both. The former is considered more likely. An angiocardiogram performed subsequently from the right median basilic vein demonstrated a right superior vena cava but failed to show any communication with the left superior vena cava (Fig. 4).

CASE 3. This 31-year-old man was admitted to the hospital because of epigastric distress and during hospitalization a roentgenogram of the chest revealed right atrial enlargement. This was confirmed by fluoroscopic examination. The electrocardiogram showed an incomplete right bundle branch block. During cardiac catheterization performed from the left arm, the catheter passed downward along the left border of the cardiac silhouette and then curved toward the right to enter the right atrium. The right ventricle and pulmonary artery could not be entered. A second catheterization was performed later through the right antecubital vein. The catheter was passed down the right superior vena cava into the right atrium and then through the coronary sinus to the left superior vena cava. During the course of the catheterization an anomalous pulmonary vein was entered from the right superior vena cava. (A blood sample at this site was 95 per cent saturated with oxygen.) Pressures obtained from the pulmonary artery and right ventricle were normal. The increased oxygen saturation noted in blood samples obtained from the right atrium could be explained by the anomalous pulmonary venous drainage, although the possibility of an atrial septal defect in addition could not be excluded.

DISCUSSION

In order to appreciate the nature of the various anomalies of the superior vena cava system, an understanding of its embryology[12-14] is essential and therefore will be briefly presented. At an early embryonic stage, (Fig. 5, *A*), the paired precardinal veins return the blood from the primitive segments which will later form the head, neck, and upper extremities. The paired postcardinal veins return the blood from the caudal segments. The precardinal and postcardinal veins join to form the common cardinal veins (ducts of Cuvier) and both common cardinal veins empty into the sinus venosus which drains into the heart. The sinus venosus itself originally arises by a constriction from the hind end of the common atrium. As the heart develops, the sinus venosus becomes located on the dorsal wall of the atrium. Eventually, the right portion (right cornu) of the sinus venosus is incorporated into the right atrium, while the transverse portion of the sinus venosus is destined to form the coronary sinus. The left portion (left cornu) of the sinus venosus gradually disappears except for its tip which becomes the stem of the oblique vein of the left atrium. During the eighth fetal week, the right and left precardinal veins become connected by an oblique venous channel (left innominate vein) which shunts blood across to the right (Fig. 5, *B*). The left precardinal vein then gradually disappears with only its uppermost portion persisting as the highest left intercostal vein. The left common cardinal vein decreases greatly in size and forms most of the oblique vein of the left atrium. The right common cardinal vein and right

precardinal vein form the right superior vena cava draining to the right atrium. By the sixth fetal month, the left cardinal venous system is usually completely involuted (Fig. 5, *C*).

If the anastomosis between the right and left precardinal veins fails to develop or if the anastomosis is inadequate, the left cardinal system may remain as a persistent left superior vena cava* draining to the right atrium via the coronary sinus. If the anastomosis runs obliquely downward from right to left (instead of left to right), the right cardinal system may involute leaving only a left superior vena cava to drain the upper body. If there is a faulty development of the interatrial septum, a persisting left superior vena cava may drain to the left atrium. Since there are early embryonic connections between the pulmonary venous system and the cardinal system of veins, one may occasionally encounter a persistent left superior vena cava which drains one or more of the pulmonary veins (Case 1).[8,15]

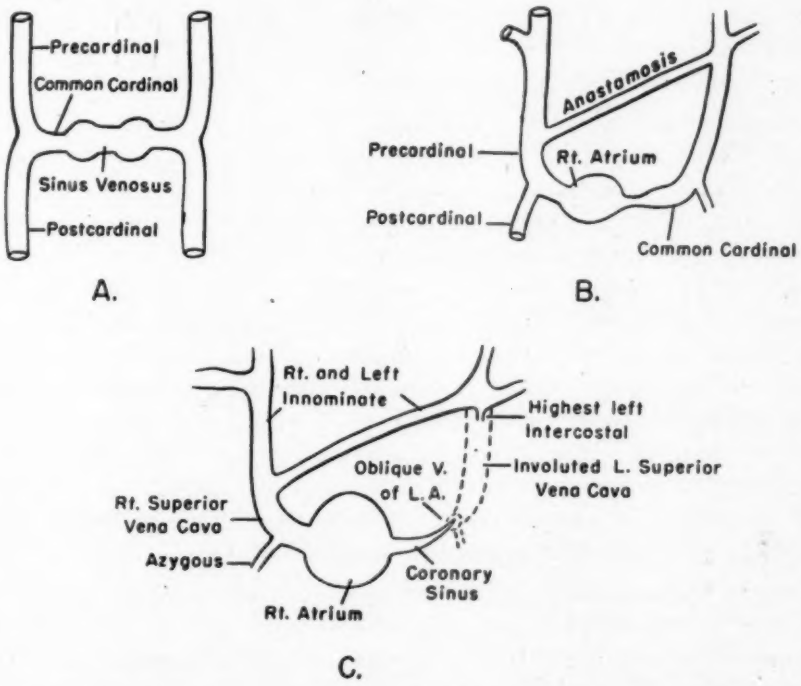

Fig. 5.—Normal developmental stages of the superior vena cava. *A*, The pre- and post-cardinal veins join to form the common cardinal veins (ducts of Cuvier) which empty into the common atrium via the sinus venosus. *B*, An anastomosis (left innominate vein) forms between the precardinal veins. The right portion of the sinus venosus has been taken up by the right atrium while the transverse portion will form the coronary sinus. *C*, Final state. The left precardinal vein (left superior vena cava) has involuted. The left horn of the sinus venosus and the left common cardinal vein form the oblique vein of the left atrium.

The exact incidence of a persistent left superior vena cava is unknown. It is also uncertain whether the condition is more frequently found in association with other congenital cardiovascular anomalies. Whereas the early post-mortem

*Numerous other theories have been presented to explain the origin of this anomaly, but the one given appears to be most widely supported.

reports rarely mention associated malformations, most of the recent cases have been inadvertently found in patients being investigated for congenital heart disease. It appears clear, however, that the occurrence of a left superior vena cava is not rare. Castellanos encountered forty-one cases between 1947 and 1950 while our first two cases (Case 3 was studied at Brooke Army Hospital) were observed in the course of the first twenty-four catheterizations performed in patients with congenital heart disease at out institution.

Of what practical significance is a persistent left superior vena cava? If the vein drains into the right atrium by way of the coronary sinus, as it usually does, there is no additional strain whatever placed on the heart and there is no abnormal admixture of venous and arterial blood. However, if the patient also has an additional congenital cardiac anomaly, a left superior vena cava may occasionally obstruct the approach at the time of surgery.[3,9] In such a case it would be of great practical importance to know whether a right superior vena cava was also present and whether the two venae cavae were connected. If such an anastomosis existed or could be constructed, the left superior vena cava could then be sectioned whenever necessary.

When one or more anomalous pulmonary veins enter a persistent left superior vena cava which empties to the right atrium, the condition is similar to that which exists when anomalous pulmonary venous drainage occurs directly to the right atrium or to any of its tributaries. When the anomalous pulmonary venous drainage is not of great magnitude, surgical treatment is not indicated at present, but when an entire lung or more drains to the right side, surgery may sometimes be performed.[16] Thus if corrective procedures should be contemplated at some time in the future in our first patient (atrial septal defect and persistent left superior vena cava probably receiving anomalous pulmonary veins,) it would be essential to determine whether any anastomosis existed between the superior venae cavae. Such information would be vital should ligation of the left superior vena cava be necessary at the time of surgery. The presence or absence of venous connections between the superior venae cavae can usually be determined by angiocardiography.[3]

Rarely the left superior vena cava may drain to the left atrium.[7,8,17,18] This anomaly per se constitutes a significant abnormality, since it is a form of right-to-left shunt causing an admixture of venous and arterial blood in the left atrium. Diaz and associates[18] reported the first successful ligation of a left superior vena cava entering the left atrium in a patient with the tetralogy of Fallot and an atrial septal defect. They considered the patient's postoperative improvement to be spectacular. Feindt and Hauch[7] also ligated with good results a left superior vena cava which emptied into the left atrium.

A left superior vena cava is of additional importance to those engaged in catheterization studies. In general, it is extremely difficult to maneuver the catheter into the pulmonary artery when the catheter enters the right atrium via the coronary sinus (Fig. 2). It is often necessary to perform an additional catheterization from the right arm (if there is a right superior vena cava) to obtain satisfactory diagnostic data. We were able to enter the pulmonary

artery in only one of our three cases when catheterizing from the left arm while Friedlich and associates[5] successfully reached the pulmonary artery in only two of eleven cases.

A review of the embryologic development of the superior vena caval system readily explains the numerous variations of persistent left superior vena cava which may occur. An extensive classification may be given but the essential variables are as follows: (1) the presence or absence of the right superior vena cava, (2) the presence or absence of an anastomosis between the two superior venae cavae, (3) the type of anastomosis which exists; i.e., a single channel or venous plexus, (4) the chamber into which the left superior vena cava empties; i.e., left or right atrium, (5) the presence or absence of anomalous pulmonary venous drainage to the left superior vena cava, and (6) the presence or absence of other cardiovascular anomalies.

It is generally impossible to make a diagnosis of persistent left superior vena cava on the basis of clinical findings alone. The vein will usually not be of sufficient density to be demonstrated on routine roentgenograms unless most or all of the pulmonary veins drain into it.[19] The diagnosis of persistent left superior vena cava is readily established when angiocardiography is performed from the left arm, and the site of the anomalous drainage can be clearly visualized. If there is an adequate anastomosis between the two superior venae cavae, angiocardiography from the right arm may also demonstrate a persistent left superior vena cava, although not as clearly as when the injection is made from the left. The characteristic course taken by a cardiac catheter which enters the heart via a persistent left superior vena cava may be clearly seen in Figs. 1 and 3. The advantages of angiocardiography in these cases are that it may delineate the actual size of the venae cavae and demonstrate the presence and nature of any communications between them. Cardiac catheterization, on the other hand, permits a more complete study of the existing cardiovascular dynamics which may be essential for the diagnosis of additional congenital cardiac anomalies present in a particular case. At times both angiocardiography and cardiac catheterization will have to be performed in order to establish a complete diagnosis.

As with other congenital cardiovascular conditions, the persistence of the left superior vena cava has gradually progressed from the sphere of "academic interest" to a position of more practical concern to those engaged in the study and treatment of congenital heart disease.

SUMMARY

Three cases of persistent bilateral superior venae cavae diagnosed by cardiac catheterization have been presented. The embryologic development of the superior venae cavae has been reviewed. When the left superior vena cava empties into the right atrium via the coronary sinus, there is no change in circulatory dynamics such as occurs when drainage is to the left atrium. The practical significance of a persistent left superior vena cava is considered.

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Clinical Reports

A CASE OF COARCTATION OF AORTA AT AN UNUSUAL SITE

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COARCTATION of the aorta is not uncommon, but the stenosis of the aorta beyond the isthmus is rare. So far about one and one-half dozen cases have been reported (Table I).

TABLE I. REPORTED CASES OF COARCTATION OF AORTA AT UNUSUAL SITES

AUTHOR	YEAR	SITE OF COARCTATION
Schlesinger[1]	1835	Thoracic aorta near the diaphragm
Power[2]	1861	Abdominal aorta below the origin of visceral arteries
Hasler[3]	1911	Thoracic aorta 3 cm. above diaphragm
Costa[4]	1930	Thoracic aorta between the origin of first and second intercostal arteries
Hickl[5]	1931	Thoracic aorta just below the isthmus of the aorta
Hahn[6]	1933	Thoracic aorta at the level of the diaphragmatic dome
Schleckat[7]	1933	Thoracic aorta
Maycock[8]	1937	Abdominal aorta 1.5 cm. below the origin of the renal arteries
Baylin[9]	1939	Abdominal aorta just distal to the origin of the renal arteries
Steele[10]	1941	Abdominal aorta just above and at the level of the renal arteries
Steele[11]		Abdominal aorta just below diaphragm
Olim[12]	1941	Thoracic aorta 5 cm. above diaphragm
Bahnson et al.[13]	1949	(1) Abdominal aorta below the origin of renal arteries (2) Mid-thoracic aorta
Beattie et al.[14]	1951	Thoracic aorta at the level of the diaphragm
Brock et al.[15]	1952	Thoracic aorta just above diaphragm
Glenn et al.[16]	1952	Lower thoracic and upper abdominal aorta
Deterling[17]	1953	Lower thoracic aorta

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CASE REPORT

We record a case of coarctation of the thoracic aorta in a female patient aged 13 years. The patient was admitted to the hospital on Nov. 24, 1953. She was quite well and active till the age of eleven, when for about a year she suffered from attacks of irregular fever and sore throat. Her tonsils were removed. A few months later she noticed that she became breathless on accustomed exertion. Subsequently, she complained of weakness, palpitation, and a sense of warmth in upper limbs, and coldness in legs and feet. She also had shifting pains in knee and wrist joints.

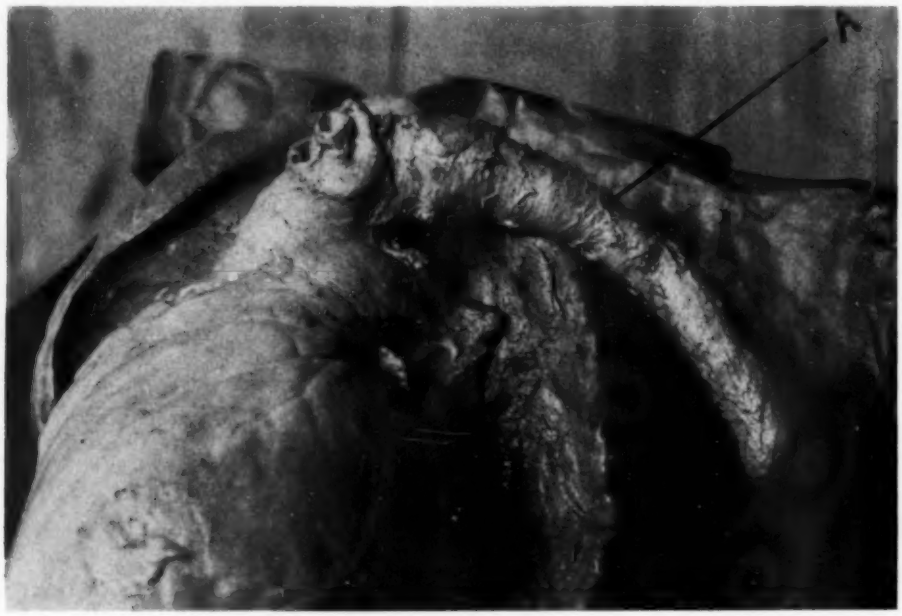

Fig. 1.—Constriction of thoracic aorta beginning at 4.5 cm. beyond the origin of left subclavian artery (*A*).

The dyspnea, palpitation, and weakness gradually progressed, and she was confined to bed for two months before her admission in the hospital. During this period she had two attacks of paroxysmal dyspnea. There was no significant past or family history.

The patient was stunted in growth and anemic. There was no cyanosis, jaundice, or edema. Pulsations of the carotids were vigorous. A prominent pulsation was noted in the suprasternal notch. Neck veins were not engorged. Temperature, 98° F. Pulse, 110 and respiration 24 per minute. Radial and brachial arteries were thickened. The pulse was regular and of high tension. No pulsations could be felt in the abdominal aorta or in the femoral, popliteal, posterior tibial, and dorsalis pedis arteries. Blood pressure in the right arm was 250/140 mm. Hg and on the left side 245/145 mm. Hg. It could not be detected in the lower limbs due to absence of the Korotkov's sounds. A feeble pulsation was felt over the thickened posterior tibial arteries when the pressure in the manometer cuff applied over the thigh was lowered to 140 mm. Hg. The apical impulse was in the fifth left intercostal space three-fourths inch outside the midclavicular line. It was heaving in character. No thrill was present. The mitral first sound was loud. A localized loud systolic murmur was heard over the left second intercostal space one inch from the sternum. The pulmonary second sound was accentuated and split. The aortic second sound was ringing, and a soft systolic murmur was present in this area. A systolic murmur was also heard over the lower part of the left interscapular area. There were no collateral vessels in the chest or back. The liver and spleen were not palpable. There was no ascites. A few crepitations and rhonchi were heard over both lungs. Ophthalmoscopic examination showed blurring of disc margins, retinal arteriolarsclerosis, and superficial hemorrhages and exudates which arranged themselves in a star-shaped fashion. No abnormalities were detected in other systems.

Investigations: Blood, hemoglobin 10.5 gram per cent; red cells, 3,820,000 per cu. mm.; white cells, 6,500 per cu. mm.; erythrocyte sedimentation rate (Westergren) 46 mm. per hour. Urea, 24 mg. per cent; nonprotein nitrogen, 26 mg. per cent; cholesterol, 111 mg. per cent; calcium, 10.5 and phosphate 3.9 mg. per cent. Wassermann reaction of blood was negative. No abnormalities in urine or stool. Skiagrams of chest did not show any notching of ribs. The left ventricle was enlarged. Angiocardiography could not be done. Electrocardiograms showed evidences of left ventricular strain.

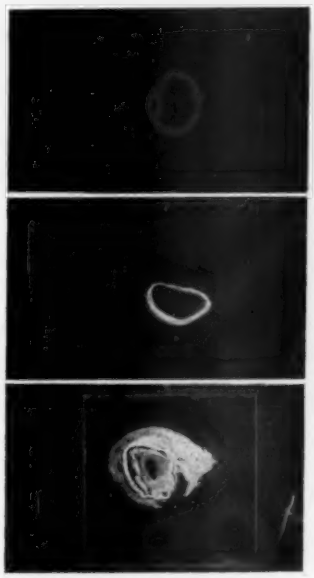

Fig. 2.—*A*, Left common carotid artery at its origin (natural size). Intima thickened with atheromatous changes in it. *B*, Left subclavian artery at its origin (natural size). Intima thickened with atheromatous changes in it. *C*, Thoracic aorta at the level of the diaphragm (natural size). The wall markedly thickened and lumen narrowed.

With rest in bed, the patient was relieved of dyspnea and palpitation. Her general health improved. The pulse rate came down to 100 per minute. During observation in the hospital the systolic pressure varied between 235 and 255 mm. Hg and the diastolic between 135 and 150 mm. Hg.

On Dec. 24, 1953, she was operated on by Dr. A. K. Basu under gas, oxygen, intermittent positive pressure anesthesia administered by Dr. S. N. Chatterjee. The left thoracic cavity was entered through the bed of the left fifth rib after resection of its whole length. The anterior and posterior ends of the fourth rib were divided. The left lung was retracted anteriorly, and the thoracic aorta was exposed. An incision was made on the mediastinal pleura covering the aorta, and the flaps were mobilized and held away by anchoring sutures. The aorta was carefully dissected. No constriction was evident at the usual site for coarctation. Starting, however, at the midthoracic region and extending to the diaphragm, the descending aorta was constricted and thickened. The mediastinal pleura was firmly adherent to this segment of the aorta. As it was considered not feasible to resect the whole area, the operation was abandoned. The thorax was closed with a drain inside the cavity.

At the end of the operation, when she was turned flat she was found to be cyanosed and dyspneic and both lungs were full of râles. The heart was beating very forcibly; pulse, 140; respiration, 32 per minute. She was treated with oxygen, digitalis, and Pethidine. Frothy material was aspirated from the lungs. Though she survived from the acute left-ventricular failure, she remained very ill until her death at 3 A.M. of Dec. 30, 1953. She remained conscious

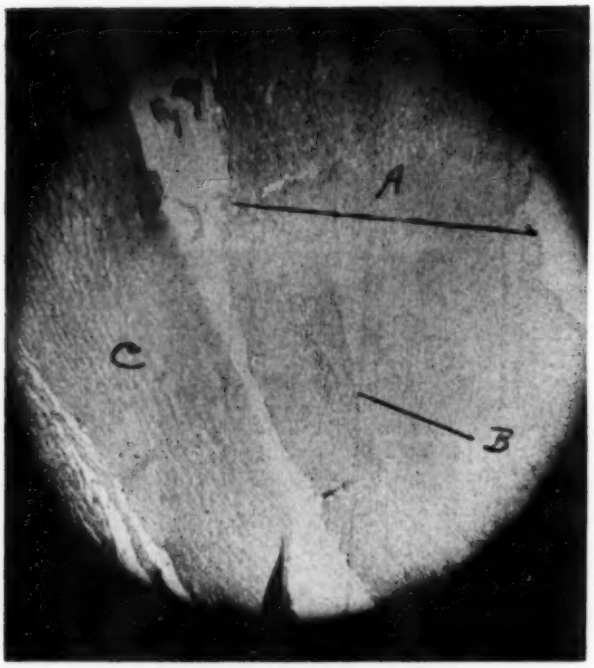

Fig. 3.—Intima (*A*) markedly thickened. Deposits of lipoid material (*B*) in intima. Media (*C*) thickened and split.

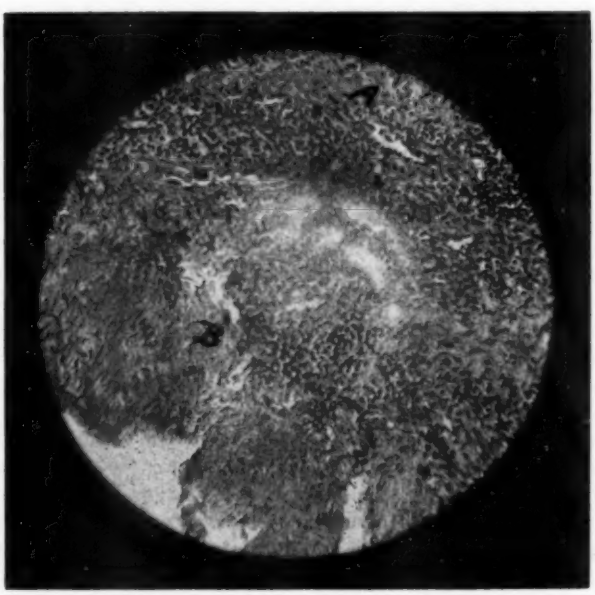

Fig. 4.—Perivascular round-cell infiltration in media (*A*) and adventitia (*B*).

until 2 hours before her death. Heart rate varied between 130 and 160 and systolic blood pressure 230 and 260 mm. Hg and diastolic 120 and 140 mm. Hg. During the last two days of her life, her extremities were icy cold, and she perspired profusely.

A partial *autopsy* was allowed. The left ventricle was enlarged and markedly hypertrophied. There were no congenital lesions in the heart.

Coarctation of the thoracic aorta began 4.5 cm. beyond the origin of the left subclavian artery and extended to the level of the diaphragm measuring 8.5 cm. (Fig. 1). Girths of the aorta at different levels were as follows: root, 7.8 cm.; just beyond the origin of the left subclavian artery, 6.1 cm.; just above and at the beginning of the coarctation, 5.6 and 4.5 cm.; at the level of the diaphragm, 3.4 cm. The thickness of the wall and the size of the lumen of the left common carotid and subclavian arteries at their origin and of the aorta at the level of the diaphragm may be seen in Figs. 2, A, B, and C, respectively. On microscopic examination, the constricted portion of the aorta showed thickening of the intima and early artheromatous changes in it (Fig. 3). There was perivascular round-cell infiltration in media and adventitia (Fig. 4). Athermomatous changes were also found in left subclavian and common carotid arteries.

DISCUSSION

Though coarctation of the aorta at the usual site is more common in the male sex, all the cases of stenosis of the aorta below the isthmus except that reported by Schleckat[7] were in the female sex.[17] Notching of ribs as made out in a skiagram of the chest was usually absent. In all the cases of stenosis of descending aorta except that reported by Costa,[4] the constriction was diffuse.[13] Our patient was a female. Her skiagram of the chest did not show any notching of the ribs. As a partial autopsy was done, the exact length of the constriction could not be noted. To the level of the diaphragm it measured 8.5 cm.

The genesis of coarctation of the aorta at unusual sites is obscure. In our case the constricted portion of the aorta was hard, thickened, and adherent to the mediastinal pleura. There was perivascular round-cell infiltration in media and adventitia. Wassermann reaction of the blood was negative. She gave a history of repeated attacks of sore throat and pains and aches in knee and ankle joints. It is, however, not possible to state if these were rheumatic manifestations. The marked thickening of the constricted portion of the aorta and round-cell infiltration of media and adventitia suggest an inflammarory origin of the lesion. The possibility of inflammatory changes taking place over a congenital lesion can not, however, be excluded.

In coarctation of the aorta, angiocardiography usually shows the site and length of the constriction. This investigation is particularly important in female patients and in cases showing unusual features like absence of visible collateral arteries in chest and back and of rib notching in skiagrams of the chest.

SUMMARY

A case of coarctation of the thoracic aorta in a female patient aged 13 years has been described.

Importance of female sex, of absence of visible collateral vessels in chest and back, and of rib-notching in a skiagram of the chest in the diagnosis of this type of coarctation has been discussed. The nature of the lesion has been discussed.

We are grateful to Dr. A. K. Dutta Gupta, Principal-cum-Superintendent, Nilratan Sircar Medical College and Hospital, for the permission to publish this case, and to Prof. S. N. De for pathologic reports. Our thanks are due to Dr. S. N. Chatterjee for administering anesthesia, to Prof. S. Bose and Dr. R. Roy Chaudhury of the Department of Radiology and to Drs. S. Masud and B. Sen Gupta, House Physicians to the Associate Professor of Medicine for their help in the investigation of the case, to Drs. B. Mukherjee, R. Roy and S. Neogy, of the Department of Surgery, for their help during operation and postoperative period, to Dr. D. Basak for referring the case to us, and to Messrs. K. Das Gupta, K. Das, and M. Mazumder for the photographs and photomicrographs.

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A CASE OF DOUBLE AURICULOVENTRICULAR BLOCK WITH AN IDIOVENTRICULAR RATE OF 14 PER MINUTE AND "CHAOTIC" AURICULAR ACTIVITY

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IN view of certain remarkable electrocardiographic features, the following case report is considered worthy of publication.

CASE REPORT

A Punjabi male, aged 70 years, had been under treatment for hypertension for many years. Apart from occipital headaches, nocturia, and dyspnea of effort, he had been singularly free of symptoms. In October, 1953, and again in January, 1954, he had been successfully treated for left ventricular failure.

The following investigations had been carried out in January, 1954. The urine was normal except for a trace of albumin and a few, scattered hyalogranular casts. Blood Wassermann and Kahn reactions were negative. The blood counts were normal, except for a mild degree of normocytic hypochronic anemia. The blood urea was 36 mg. per 100 c.c. Fluoroscopy revealed a bootshaped heart with massive hypertrophy of the left ventricle, a widely unfolded and sclerotic aortic arch, and bilaterally prominent hilar shadows.

There was nothing of importance in the family or past history of the patient.

On March 20, 1954, at 11 A.M., he suddenly lost consciousness, went "blue in the face" and had a convulsion, the whole episode lasting only a minute or two. These momentary lapses of consciousness with convulsive manifestations continued to recur, at intervals of minutes or hours, until the time of death. In view of a slow but regular pulse and cardiac rate of 28 per minute, he was diagnosed as a case of complete heart block with Stokes-Adams syndrome.

A clinical examination on March 21, 1954, revealed an old and undernourished man of hyposthenic habitus, with dyspnea even at rest, and edema of both legs. The neck veins were engorged and pulsating independently of the apical impulse, the liver was tender and palpable 2 inches below the right costal margin. The pulse, which was full and bounding, was regular and 28 per minute. The respiration rate was 28 per minute. The blood pressure was 186 mm. Hg systolic and 74 mm. diastolic.

The apex impulse, diffuse and heaving, was seen and felt in the sixth left intercostal space, in the anterior axillary line. A diastolic "shock" was palpable in the aortic area. On auscultation, a systolic bruit was heard all over the precordium, the first sound was reduplicated at the apex, while the second sound was "metallic" and markedly accentuated in the aortic area; soft auricular sounds were audible, over the third and fourth left intercostal spaces, during the long pauses between the normal heart sounds. Since the patient lived in a suburb of Bombay, an

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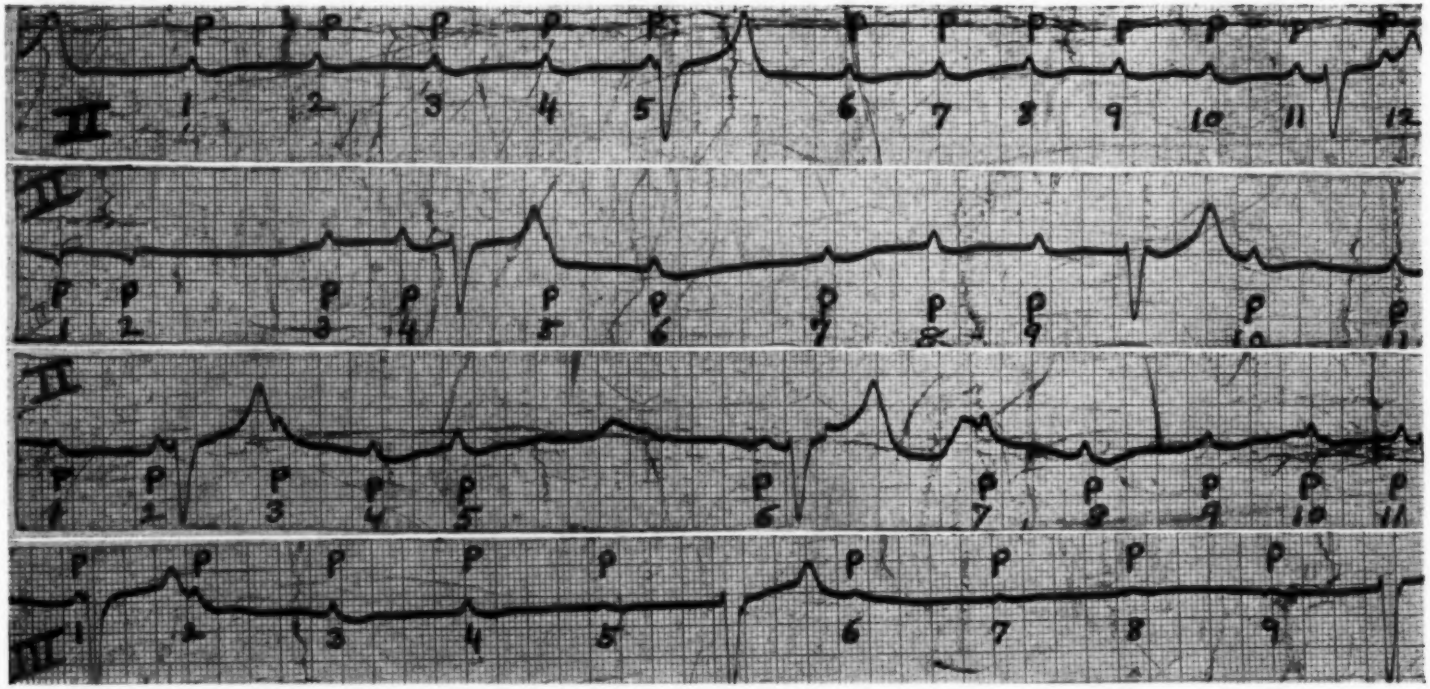

Fig. 1.—Electrocardiographic record of the standard extremity leads. The QRS-T complexes occur regularly at a rate of 14 beats per minute. The auricular waves, which are marked "*P*" and numbered, wherever discernible, show irregularities of contour, direction, and spacing, indicative of "chaotic" auricular activity, with arrhythmia and "wandering" of the cardiac pacemaker.

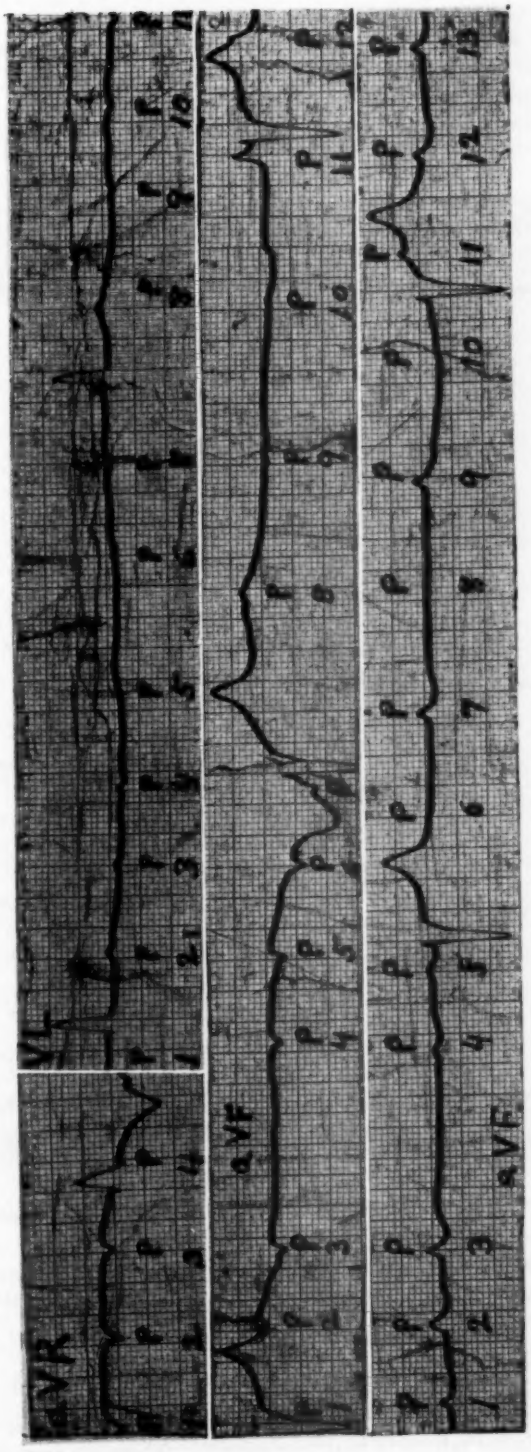

Fig. 2.—Electrocardiographic record of the unipolar extremity leads.

electrocardiographic tracing was not possible, on that day. He was put on ephedrine sulphate, ½ grain, and atropine sulphate, 1/100 grain, by mouth, every 4 hours.

He was re-examined, at 1 P.M., on March 23, 1954, in view of a complaint of severe throbbing in the chest. The clinical findings were no different from those of March 21, 1954, except for the pulse and cardiac rates, which were both 14 per minute and regular, instead of the previous 28 per minute. An electrocardiographic tracing, obtained at this time, is reproduced (Figs. 1, 2, and 3).

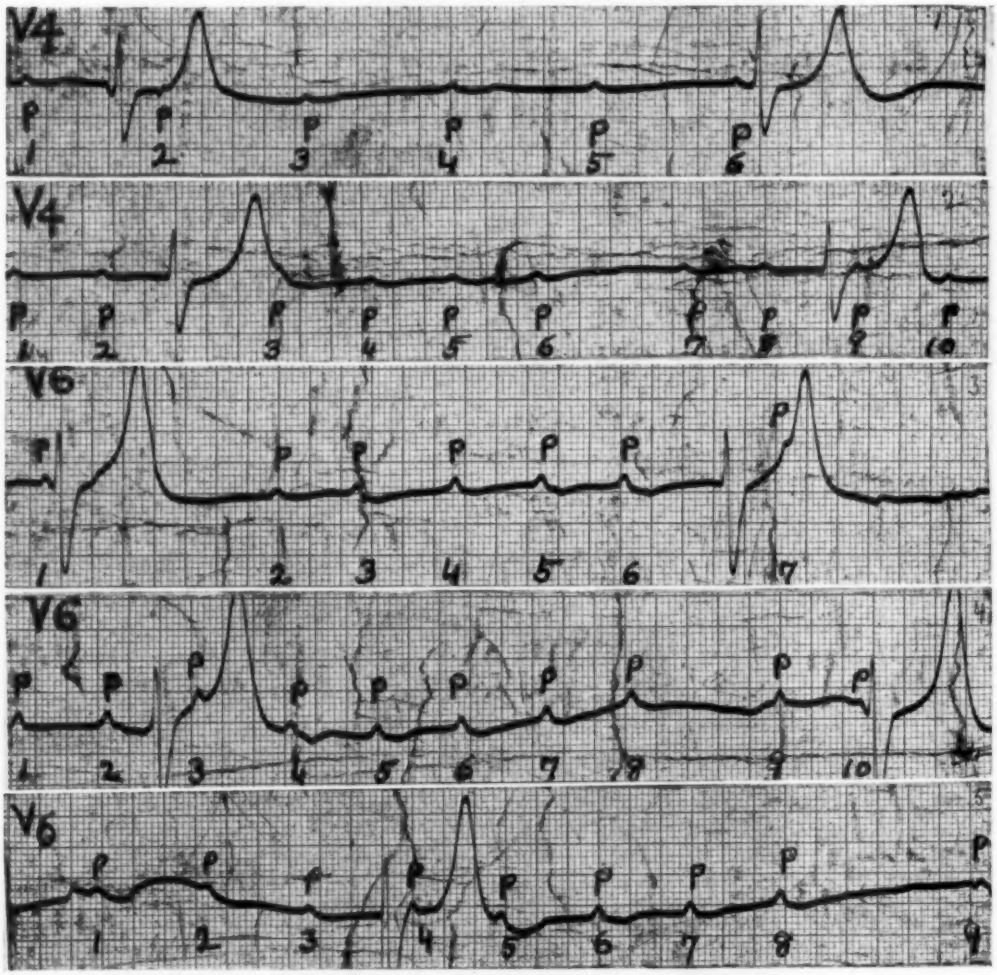

Fig. 3.—Electrocardiographic record of the unipolar chest leads.

In spite of the persistently slow rate of the ventricle and frequent seizures of Stokes-Adams type, the patient's condition remained unchanged until 3 P.M. on March 25, 1954, when he expired suddenly during one of his seizures.

ELECTROCARDIOGRAPHIC INTERPRETATION

Throughout the record, the ventricular complexes occur at regular intervals of 4.2 seconds, equivalent to an idioventricular rate of 14 beats per minute. There is a complete lack of relationship between the P waves and QRS-T complexes. In view of these facts, a diagnosis is justified of complete A-V heart block, with an unusually slow rate of beating. In view of the increased

duration of QRS (0.17 second) with slurring and abnormal configuration, the idioventricular pacemaker can be located below the level of bifurcation of the A-V bundle. The sudden drop of idioventricular rate from 28 per minute to 14 per minute (or exactly one-half), during the course of the illness, raises the possibility of a superadded 2 to 1 or partial idioventricular block.

Of unusual interest, also, is the erratic behavior of the P waves throughout the record. A gross degree of sinus arrhythmia is apparent throughout, there being sinus bradycardia at one extreme and sinus tachycardia at the other. Certain P-P intervals in the record (viz., P_5 to P_6 of strip *A*, P_6 to P_7 of strip *B*, P_5 to P_6 of strip *D*, P_3 to P_4 of strip *H* and P_6 to P_7 of strip *J*) are examples of sinoauricular block, being twice the length of normal P-P intervals. Similar but longer P-P intervals with no mathematical relationship to normal P-P intervals (e.g., P_5 to P_6 of strip *C*, and P_1 to P_2 of strip *K*) represent so-called "sinus pauses."

Alterations in the contour or configuration of upright P waves of sinus origin are observed throughout the record, particularly in strips *B*, *D*, and *M*, and are indicative of a "shifting" or "wandering" of the pacemaker within the sinus node. On the other hand, grosser degrees of contoural alteration of P waves, e.g., from normal and upright P waves of sinus origin to inverted and retrograde P waves of A-V nodal origin, as seen in strips *F*, *G*, and *H*. These are evidence of wandering of the pacemaker between the sinus and A-V nodes. It is a matter for conjecture whether certain P waves in the electrocardiographic tracing (e.g., P_5, P_6, and P_7 of strip *F*, and P_8, P_9 and P_{10} of strip *G*), which are intermediate between upright P waves of sinus origin and inverted P waves of nodal origin, should be regarded as "auricular fusion beats" or as indicative of a shift of the pacemaker to a lower site within the sinus node. In strip *F*, three distinct types of P waves are observed (P_2 to P_4 being upright, P_9 to P_{11} inverted, and P_5 to P_8 intermediate in form). P_6 to P_{11} in strip *H* exhibit an unusual variety of "electrical alternans," large and upright P waves alternating regularly with small and almost isoelectric P waves, suggestive of two pacemakers working alternately, in orderly sequence. While prematurely occurring upright P waves of abnormal contour (e.g., P_3 and P_4 of strip *B*, P_2 and P_3 of strip *H*) are examples of auricular premature beats, similar but inverted or retrograde P waves, occurring prematurely (e.g. P_1 and P_2 of strip *B*), may be examples of nodal premature systoles. By assuming this to be correct, couplets P_1 to P_2 and P_3 to P_4 of strip *B* may be regarded as examples of the rare phenomena of "paired nodal" and "paired auricular" extrasystoles, respectively. Strip *A* illustrates yet another electrocardiographic phenomenon, viz., that of "warming up" or "accleration" in the rate of discharge of the sinus node, after a ventricular complex. The opposite phenomenon of "slowing down" of the rate of discharge after a ventricular complex is seen in strip *B* (P_8 to P_{11}).

DISCUSSION

In spite of the natural or inherent rate of impulse formation of the idioventricular pacemaker, in cases of complete auriculoventricular heart block, being usually 28 to 36 per minute, rates of below 20 per minute have been reported from time to time. As early as 1793, Spens[1] reported a rate of 9 beats per minute.

Extreme slowing of ventricular action, as a transitory or momentary phenomenon, is not uncommon, during seizures of Stokes-Adams type, or during the transition phase between different grades of block, or as a preterminal event.[2]

On the other hand, persistent idioventricular rates of below 16 per minute are extremely rare. An interesting but rare variant of complete heart block is the condition of *double atrioventricular block*[3,4] or *block within block*,[5] where a state of partial (usually 2 to 1) idioventricular block is superimposed on the complete A-V block. Cases of this type have been reported, in the past, by White[3] and by Langendorf and Katz.[4] The present case of complete heart block, with a sudden halving of the idioventricular rate from 28 to 14 per minute during the course of the illness, rightly belongs, therefore, to this category. The persistence of "double A-V block" for over forty-eight hours in this case, without any "lifting" of the block, was unusual.

Auricular arrhythmia or irregular auricular action has been reported on numerous occasions in cases of both complete and partial auriculoventricular block. Erlanger and Blackman[6] first noted its existence in experimental heart block. Its existence as a clinical entity was first reported, by Hecht[7] in 1914.

The mechanism of production of auricular arrhythmia in cases of heart block has been the subject of numerous hypotheses. It has been assigned to increased vagal tone by Erlanger and Blackman,[6] to the opposing effects of systole and diastole of the ventricles on the state of nutruition of the sinoauricular node by Wenckebach and Winterberg,[8] to stimulation of the pacemaker by the contracting ventricle, and to the operation of a vagus-sympathetic reflex along aortic and carotid sinus pathways by Graybiel and White[9] and by Kisch.[10] Parsonnet and Miller,[11] after a critical appraisal of various theories, assigned the auricular arrhythmia to the relative dominance of two opposing factors, viz., a depression of the pacemaker by the absence of stimuli from the contracting ventricle and a Bainbridge reflex. More recently, Roth and Kisch[12] have attributed it to reflex inhibition of the pacemaker by a rise of pressure within the aorta and carotid arteries.

The present case displays such a remarkable degree of auricular arrhythmia that auricular activity can be rightly described as "chaotic." In addition, there is a constant wandering of the pacemaker between the sinus node and the A-V node, resulting in a most unusual electroauriculogram. Close scrutiny of the electrocardiographic tracing reveals a host of electrocardiographic phenomena, viz., sinus arrhythmia, sinus tachycardia, sinus bradycardia, sinoauricular block, sinus pauses, shifting of the pacemaker within the sinus node, wandering of the pacemaker between the sinus and A-V nodes, (?) auricular fusion beats,[13] electrical alternans, auricular and (?) nodal premature beats "in pairs",[13] and postsystolic acceleration and retardation in the rate of discharge of the sinus node.

SUMMARY

A case is described, of a man of 70 years with hypertensive-arteriosclerotic heart disease, showing complete heart block with 2 to 1 idioventricular block, a ventricular rate of 14 per minute, and complete auricular arrhythmia with wandering of the cardiac pacemaker.

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HIGH VENTRICULAR SEPTAL DEFECT

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THE increased interest in congenital heart lesions and the newer and more precise methods of diagnosis have augmented our knowledge of cardiac malformations.

Among these malformations, the ventricular septal defects have been the subject of several articles[1,3-5] which besides showing the need of subdividing them into two groups, high ventricular septal defects and Roger's disease, have also helped in clarifying hemodynamics in general.

In the case we will report we had the opportunity of making a thorough clinical, hemodynamic and pathologic examination. Some of the interesting features in the differential diagnosis of maladie de Roger, high ventricular septal defect, and Eisenmenger complex will be briefly discussed.

CASE REPORT

The patient, a 3-month-old white girl, was noted since birth to be short of breath. She was born of a normal pregnancy, had a healthy sister, 3 years old, and no history of congenital defects could be elicited from the family.

Feeding had been a difficult problem, due to episodes of choking and increased breathlessness.

The pediatrician noticed a heart murmur and the x-ray showed an enlargement of the heart. She perspired profusely and had a single episode of cyanosis of the extremities.

Four days before she came under our observation she had a high temperature, diarrhea, and vomiting.

She was a pale and undernourished child, without cyanosis and with a temperature of 37° C.; pulse rate, 160, respiration rate, 70. Femoral and radial arteries were easily palpable. Blood pressure, 95/40 mm. Hg. There was a visible and forceful apex beat, slightly beyond the left mid-clavicular line. P_2 was accentuated. A thrill and a rough systolic murmur, Grade 4, were noted at the apex and the pulmonary area. At the apex the murmur seemed to start in telediastole (Fig. 1). The liver was palpable two finger breadths below the costal margin. The lungs were clear to percussion and auscultation.

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The *roentgenogram* (Fig. 2) showed a slightly enlarged and normally placed heart with a straightening of the left middle segment. The aorta was of normal caliber in the posteroanterior view, and in the left oblique view there was a question of a slight bulging of its ascending segment. In posteroanterior and right oblique views, the left auricle produced an indentation in the barium-filled esophagus. The left ventricle covered the spine in the left oblique view. The pulmonary arteries had an increased pulsation and were enlarged in the mesial one-third of the lung fields.

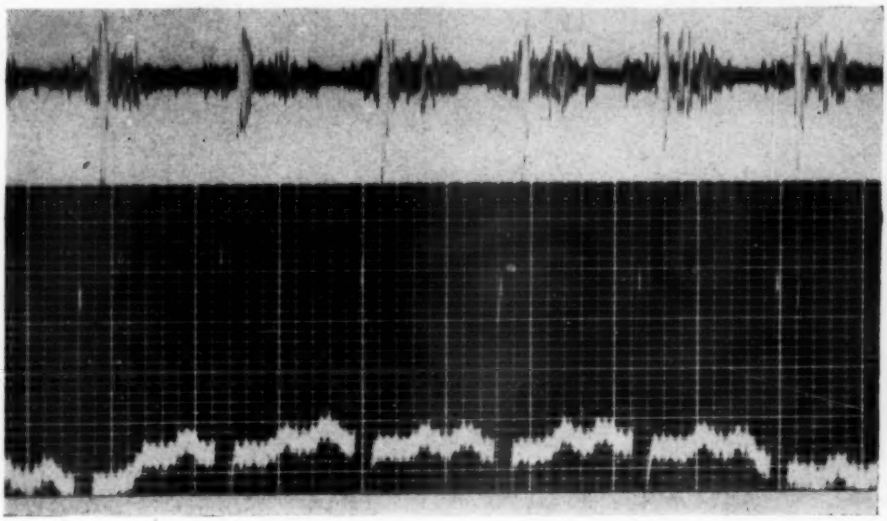

Fig. 1.—Phonocardiogram recorded at the apex. There is a presystolic and a holosystolic murmur.

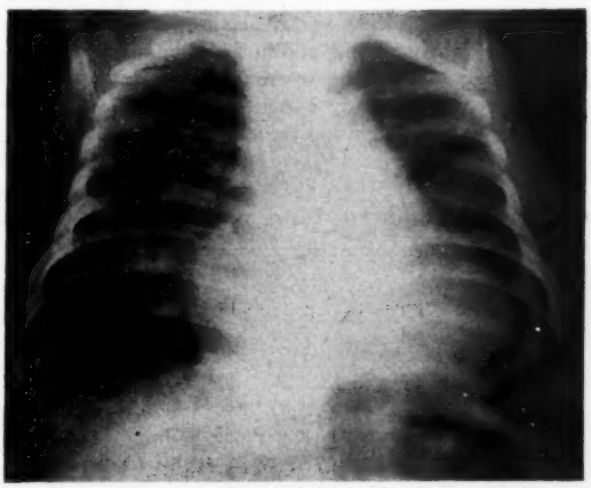

Fig. 2.—Teleroentgenogram in posteroanterior position.

The *electrocardiogram* (Fig. 3) revealed a regular sinus rhythm with normal-axis deviation. The P waves were of normal size and shape and the P-R interval was 0.08 second. The QRS complexes were tall and diphasic in Leads I, aV_R, and aV_L. In V_{3R}, V_E and V_1, there was an abnormally tall and notched R wave, followed by small S waves. In V_5 and V_6, the R waves were

also of increased voltage, although unnotched, and followed by small S waves. The S-T segment was depressed in Leads I, V_5 and V_6, and the T waves positive in all the precordial leads. These data led us to the conclusion of a double ventricular hypertrophy.

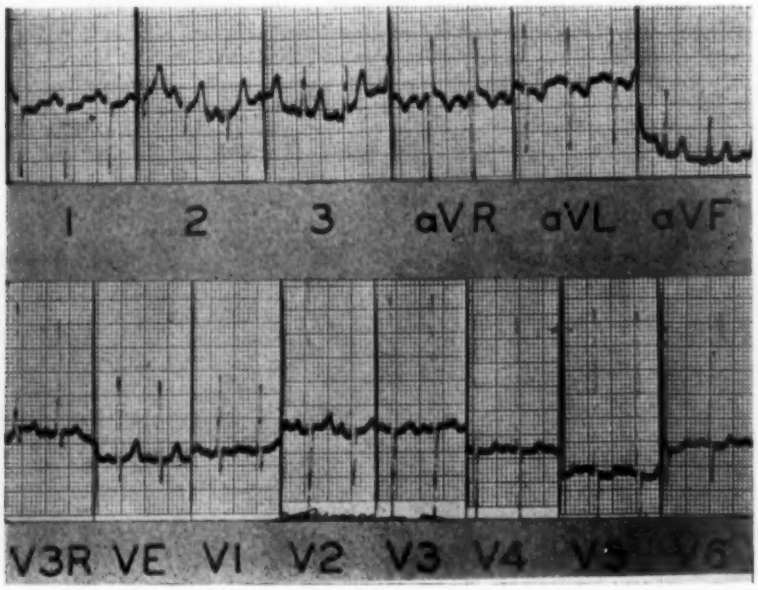

Fig. 3.—Electrocardiogram, Aug. 8, 1953. See text for details.

The catheterization of the heart was made through the saphenous route, and we were able to catheterize the aorta (Fig. 4). There was (Table I) a normal oxygen saturation in the aorta and an increased oxygen saturation in the right ventricular and pulmonary blood. Pressures were higher in the aorta than in the right ventricle, and in the pulmonary artery the diastolic pressure was very low. The pulmonary artery output was roughly five times greater than the aortic output. The normal arterial oxygen saturation and the difference in pressure between the aorta and the right ventricle led us to the conclusion that the aorta was not dextroposed. The large pulse pressure in the pulmonary artery could be attributed to a pulmonary insufficiency.

TABLE I. RESULTS OF THE CATHETERIZATION OF THE HEART

SITE	OXYGEN VALUES		PRESSURES IN MM. HG	
	VOL. %	SATUR. (%)	SYSTOLIC	DIASTOLIC
Aorta	11.76	94	71	42
R_A auricle	7.05	56		
R. ventricle	10.84	87	52	−8.8
R. pulm. art.	10.61	85	58.7	8.7
Capacity	12.4			

An *angiocardiogram* (Fig. 5), made by the same route, showed an intense dilution of the contrast medium in the right side of the heart, which seemed to start in the right ventricle.

With all this data we made the diagnosis of intracardiac communication, probably located in the ventricular septum. However, an aortic septum defect could not be excluded.

The progressive deterioration of the patient and the resistance of the heart failure to the treatment led us to resort to an exploratory thoracotomy, in the hope we could locate the defect and, if in the aortic septum, close it.

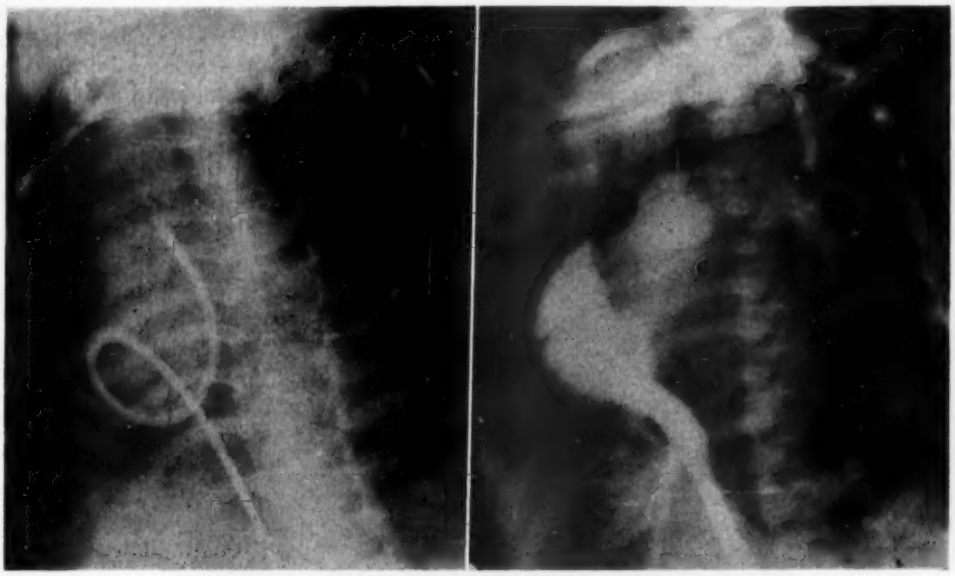

Fig. 4. Fig. 5.

Fig. 4.—X-ray of the thorax in the left oblique position with the catheter in the aorta.

Fig. 5.—Angiocardiogram in the left oblique position. There is a marked difference between the density of the contrast medium in the right cavities and the pulmonary artery.

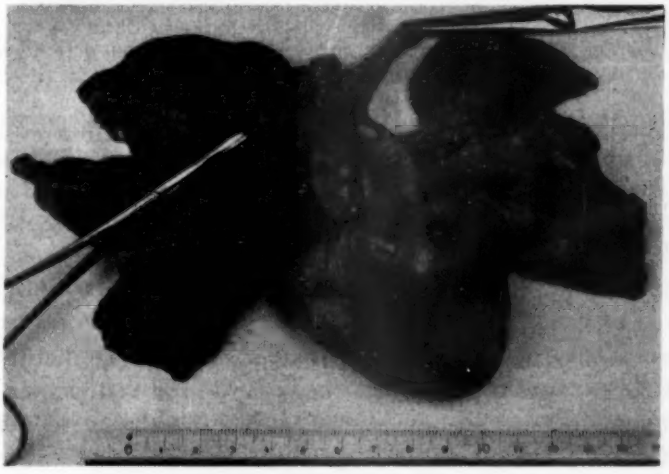

Fig. 6.—Front view of the specimen.

The operation was done by Dr. José Hilário who, upon opening the pericardium, was unable to find any abnormal communication between the aorta and the pulmonary artery. A cardiac thrill, felt during surgery, was located in the heart itself, at the base of the vascular pedicle. The heart stopped during the cardiac manipulation, and all the efforts made by the surgeon to revive it were useless.

Autopsy: Only the examination of the thoracic content was permitted. The *heart* was enlarged, with a bulging of the pulmonary conus (Fig. 6). The pulmonary artery had a normal origin and was larger than the aorta. The diameter of the pulmonary artery was 16.5 mm., and that of the ascending aorta, 14.5 mm. The ductus arteriosus was occluded. The pulmonary veins and the venae cavae were of normal capacity and had a thickened endocardium in the region of the pulmonary conus. The pulmonary and tricuspid valves were normal. There was a defect at the upper part of the ventricular septum, with an approximate diameter of 6.5 mm., circular in shape, with smooth edges, covered by a whitish and thickened endocardium, which had on the upper limit the aorta valves (Fig. 7). The left auricle was of normal shape and size. The mitral valves were slightly thickened and the mitral orifice of normal caliber. The left ventricle was of normal size. Thickness of myocardium of the left ventricle was 6.5 mm. Thickness of myocardium of the right ventricle was 3.5 mm. The coronary arteries were normal. The aorta was not dextroposed. The foramen ovale was occluded.

Fig. 7.—The left ventricle is opened and the ventricular septal defect is seen with its upper border made by the aortic leaflets.

The *lungs* had a variegated appearance in the different sections that were examined. There were zones where the alveoli were normally expanded with a clear lumen; others, with partially collapsed alveoli and, lastly, there were zones with great alteration in the alveoli, which were filled with a homogeneous substance, having the characteristics of liquid of edema and blood.

No vascular alterations were observed in the lungs.

COMMENTS

This case emphasizes the modern trend of a clear-cut distinction between "maladie de Roger", that is to say, the classical form of ventricular septal defect, and the "high ventricular septal defects".[1] While in maladie de Roger the defect is generally of small diameter, due to a perforation of the septum, with the upper border made by the septum itself, in the "high ventricular septal defects", the size is generally larger, and the upper border of the defect made by the aortic valves.

As is well known, maladie de Roger is perfectly tolerated and almost always symptomless, but the high ventricular septal defects, derived from a failure of the aortic septum to meet the ventricular septum, produce a great load on the heart, having thus a grave prognosis.

This marked difference in the clinical picture of both types of ventricular defects may be due not only to the smaller size of the defect in maladie de Roger[1,6] but also, and mainly, to the fact that in the high ventricular septal defect its higher position in the ventricular septum under the aortic valves enhances the probability of a large arteriovenous shunt.

On the other hand, the line of distinction between high ventricular septal defect and Eisenmenger complex is vague. Suffice it to say that the "princeps" observation of Eisenmenger was published as an example of interventricular septal defect, while the dextroposition of the aorta was only recognized 25 years later.[2] If, in the high ventricular septal defects with marked dextroposition of the aorta, its overriding is easily recognized, in smaller degrees of dextroposition, even experienced observers hesitate to differentiate between Eisenmenger complex and ventricular septal defect.

Realizing the difficulty in the pathologic differentiation between these conditions, several authors[2,6] have proposed to distinguish them by the presence or absence of clinical or laboratory signs of arterial oxygen unsaturation. If the aorta is "functionally" dextroposed, there should be an arterial oxygen unsaturation and, on the other hand, in "pure" high ventricular septal defects the arterial oxygen saturation should be normal.

The adoption of this hemodynamic criterion, instead of the morphologic one, lays stress on the fact that here does not exist a precise separation between those two conditions, but rather, that one merges inconspicuously with the other.

As has already been mentioned,[1,2] the Eisenmenger complex instead of an inborn disease may, in some cases, be a late phase in the development of high ventricular septal defects; the overriding of the aorta could be due to a deviation of the septum to the left or slight rotation of the aortic orifice on a posteroanterior axis. On the other hand, the progressive increase in pulmonary vascular resistance due to the great pulmonary blood flow in cases of high ventricular septal defect could eventually lead to a shunt reversal and cyanosis.

This case has served to emphasize that the mere catheterization of the aorta is not enough by itself to assure its dextroposition, unless the sampling of arterial blood presents a lowered-oxygen saturation.

The differential diagnosis between high ventricular septal defect and aortic septal defect is of great practical importance due to the possibility of surgical treatment of the latter[7] and remains a difficult one, although probably in some cases, the fluoroscopic study of the aorta may be of help in the distinction.[7] While in high ventricular septal defects the aorta receives a diminished quantity of blood, is of small caliber, and has a normal or diminished pulsation, in aortic septal defects the ascending aorta receives an increased amount of blood, is dilated, and pulsates markedly.

SUMMARY

The clinical and pathologic findings of a 3-month-old girl with a high ventricular septal defect are presented. The points of distinction between maladie de Roger, high ventricular septal defect, and Eisenmenger complex are briefly discussed.

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SEVERE ADAMS-STOKES SYNDROME TREATED WITH ISUPREL AND AN ARTIFICIAL PACEMAKER

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WHILE studying a series of cases of complete heart block under treatment with isopropyl epinephrine (Isuprel),* we had the opportunity to observe a severe case of the Adams-Stokes syndrome. This is the first case of this condition treated with the artificial pacemaker and defibrillator designed by one of us (J. R.),[1] and, as far as we can determine, the first case to be treated with intravenous infusions of Isuprel.

Nathanson and Miller[2,3] have been the strongest proponents of the superiority of Isuprel over a large number of other widely used cardiac stimulants. Their reports include the administration of the drug by all routes except by constant intravenous infusion. No other series had been published at the time this case report was prepared for publication.

METHOD AND MATERIAL

The artificial pacemaker used in this case is one that had been developed during the past year at Wayne University College of Medicine. The voltage is variable from 0 to 60 volts, and rate is variable from 20 to 200 times per minute. The entire apparatus is fitted into a cabinet 10 inch by 7 inch by 7 inch and is easily portable. The "warmup" time is negligible. Controls consist of a power switch, one dial for rate, and one dial for output voltage. There is a visual indicator for pulse rate. In addition to the pacemaker described, a defibrillator unit is incorporated within the same circuit and is operated by a push button.

Two electrode systems were used in this clinical case: an emergency and an indwelling combination. The emergency electrodes consist of a standard 21 gauge needle, a 14 gauge trochar about 3 cm. long, and an 18 gauge blunted needle about 9 cm. long. The indwelling set consists of a flexible insulated wire about 15 to 20 cm. long. The 21 gauge needle is inserted subcutaneously just below the inferior angle of the left scapula parallel to the skin. The 14 gauge trochar

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is inserted through the fourth left intercostal space in the midclavicular line, and the 18 gauge blunted needle is threaded through the trochar until it rests on the pericardium. It should not be forced into the myocardium since this is not necessary to maintain stimulation. Once the emergency set has been put into place and the pacemaker is maintaining the rate, the insulated wire can be substituted for the 18 gauge needle. The trochar can then be withdrawn, and the dangers of abrasions or extracardiac stimulation can be avoided.

The intravenous infusion of Isuprel was prepared by adding 1 mg. of the drug to 200 c.c. of 5 per cent glucose in water to make a concentration of 5 μg per ml. The rate of flow was controlled between 9 to 20 drops per minute, to supply from 3.5 to 6.5 μg per minute. Serial electrocardiograms were taken during and after the infusion.

CASE REPORT

J. W., a 55-year-old white male, was admitted with complaints of shortness of breath, weakness, swelling of the ankles, and a weight gain of ten pounds during the two weeks prior to admission. He felt that his heart beat was irregular at times and that this irregularity was related to bouts of paroxysmal nocturnal dyspnea. One week prior to admission he experienced a short period of faintness with profuse sweating but did not have chest pain, nor did he fall to the ground. Past history by systems was negative except for a peptic ulcer treated by a subtotal gastrectomy.

Physical examination revealed a male in slight respiratory distress. Blood pressure was 200/70 mm. Hg. The pulse was 28 beats per minute. Respirations were 30 per minute. Funduscopic examination showed a Grade 1 narrowing of the arterioles. Fine, moist inspiratory râles were heard at both lung bases posteriorly. The heart rhythm was irregular. A Grade 3 apical systolic murmur and a Grade 1 aortic systolic murmur were present. A nontender liver edge was palpated two fingerbreadths below the costal margin in the right midclavicular line. The extremities showed a 2+ edema.

Laboratory results: Hemoglobin 14 grams. White blood count was 9,500 with a normal differential count. Sedimentation rate 8 mm. in one hour (Westergren). Serology was negative. B.U.N. was 24 mg. per cent. Urine negative. The electrocardiogram revealed a ventricular rate of 28 with complete atrioventricular block and a complete right bundle branch block pattern.

He was treated with bed rest, mercurial diuretics, and a low-salt diet with a good response.

Serial electrocardiograms were taken after each of the following: 15 mg. of Isuprel sublingually, 0.2 mg. of Isuprel subcutaneously, and 1 mg. of epinephrine subcutaneously. There was no significant response to the sublingual Isuprel or to the subcutaneous epinephrine. The subcutaneous Isuprel increased the rate from 24 per minute to 40 per minute in three minutes. The peak rate of 45 was reached at 20 minutes. Control levels were re-established in 60 minutes.

During the first eleven days of hospitalization, cardiac compensation was restored without the use of the glycosides. The pulse ranged between 24 and 30 beats per minute, and no Adams-Stokes attacks were observed.

On the twelfth day he suddenly became cyanotic, his pulse rose to between 80 and 128, his skin became cold and clammy; then the pulse disappeared, and convulsive movements of the extremities ensued. The remainder of the patient's course is graphically represented in Fig. 1. The attacks lasted about two minutes and recurred at intervals of approximately three minutes. Administration of oxygen by nasal catheter was begun. He received 20 mg. of Isuprel sublingually, repeated in three hours, and was asymptomatic until six hours after the second dose (6:45 P.M.), when he had a series of 10 to 15 asystolic convulsions, each lasting between 50 and 70 seconds. Atropine, 1.2 mg., and Isuprel, 0.2 mg., were given intramuscularly. Thirty minutes later the pulse was 48 per minute. Twenty mg. of Isuprel were given sublingually at 7:30 P.M. Three hours later (9:40 P.M.) he had another series of 8 to 10 convulsions. Isuprel, 0.2 mg., was given subcutaneously and again in thirty minutes, and then every three hours thereafter. In spite of an injection at 3:18 A.M., his fourth series of asystolic convulsions began at 3:38 A.M. Epinephrine

0.5 mg., and atropine, 1.2 mg., were injected and the pulse resumed at 48 per minute. At 5:40 A.M., thirty minutes after another dose of subcutaneous Isuprel, the patient had his fifth series of asystolic convulsions. Again he was given 0.2 mg. of Isuprel and 0.5 mg. of epinephrine subcutaneously. Fifteen minutes later his pulse rate was 40 per minute.

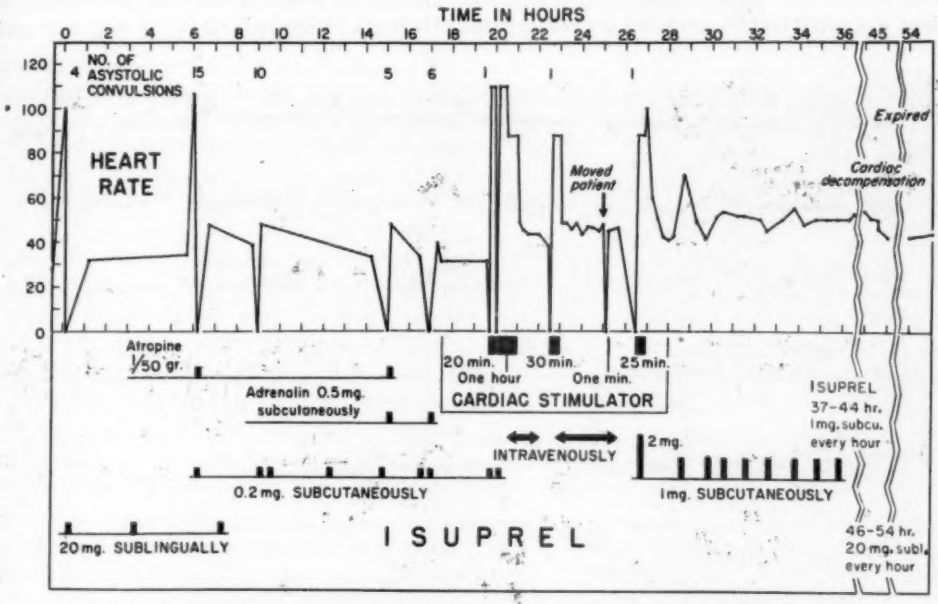

Fig. 1.—Depicts the course of patient J. W., described in the text.

At 8:25 A.M., another asystolic convulsion occurred and immediately thereafter 0.2 mg. of Isuprel was given subcutaneously. When 70 to 80 seconds had passed without a cardiac contraction, the artificial pacemaker was started. Cardiac contractions and consciousness were restored as soon as the electrodes were in place and the machine was turned on (about 40 seconds). The pulse synchronized with the visual indicator at 110 per minute. A voltage of 60 was used. There was spread of the current to the pectoral muscles and to the muscles of the left arm, producing painful spasmodic contractions. The voltage was reduced to 40 and the rate to 88 beats per minute. The twitching was then confined to the pectoralis around the trochar. When the fine insulated wire was substituted for the needle, the twitchings were eliminated. The patient was very comfortable after this change, even though the trochar was left in place for over an hour. A second dose of 0.2 mg. of Isuprel was given subcutaneously while the pacemaker was in operation. Two minutes later the machine was shut off, and the patient had a convulsion. The machine was restarted. There was an immediate response. This was repeated several times over a period of an hour with the same result.

In an attempt to establish a cardiac pacemaker, an infusion of 1 mg. of Isuprel in 200 c.c. of 5 per cent glucose was started. Two minutes after the infusion had been started, an effort to dispense with the artificial pacemaker was unsuccessful, and the patient had another convulsion. This was aborted by restarting the machine. After the intravenous Isuprel had been running for 20 minutes at a rate of 20 drops per minute, the artificial pacemaker was again shut off, and this time an idioventricular rhythm at a rate of 48 was established and maintained during the course of the infusion (60 minutes). Within 20 minutes after the infusion had been discontinued, the pulse rate had fallen ten beats per minute (Fig. 2, *A*). Twelve minutes later ventricular standstill occurred and resulted in a convulsion. The artificial pacemaker was again started with

an immediate response. A second infusion, exactly like the first one, was prepared and started while the machine was maintaining the heart rate. Twenty minutes after the intravenous infusion had been started, the electrical pacemaker was stopped and the idioventricular rhythm resumed at a rate of 48 per minute. The infusion was slowed down to 9 drops per minute (3.5 μg) and extended over a period of 150 minutes, during which the heart rate was maintained between 44 and 48 beats per minute (Fig. 2, *B* lower half). During the course of the Isuprel infusion, the patient was lifted bodily to allow for nursing care. He had another episode of asystole and again

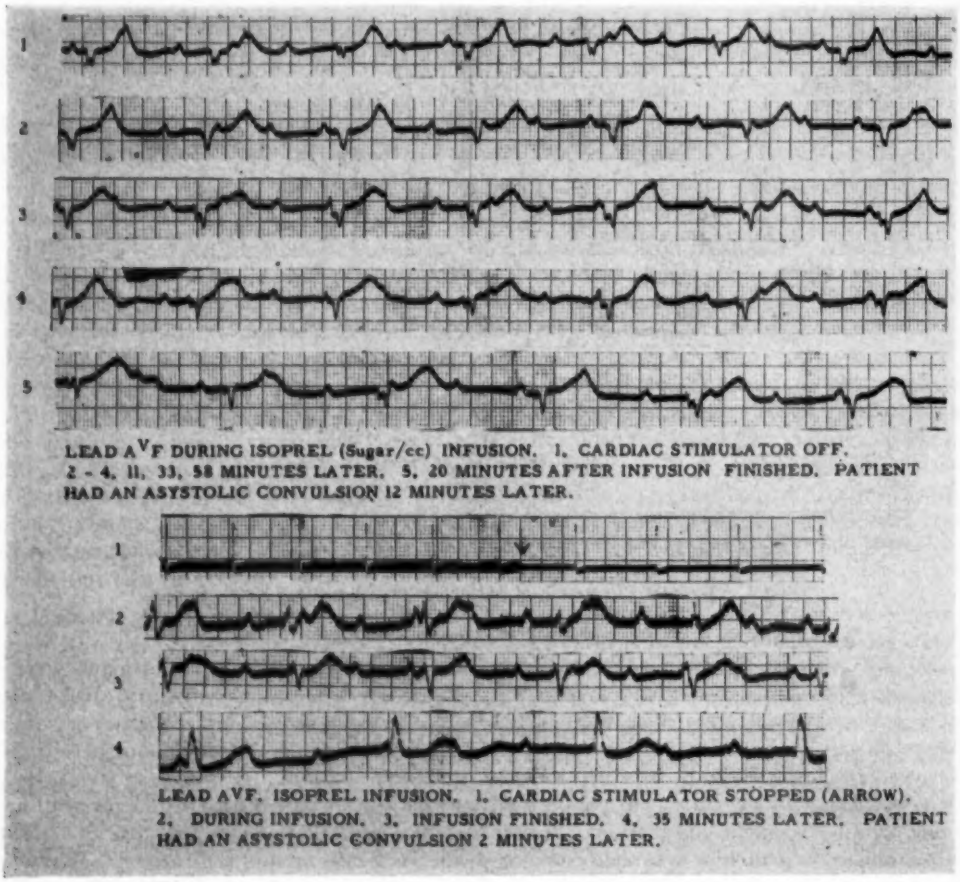

Fig. 2.

responded to the cardiac pacemaker. The machine was turned off in about one minute or less with the resumption of his cardiac rate. Thirty-five minutes after the infusion had finished, the rate had fallen to 30 per minute, and two minutes later the patient had another cardiac arrest with a convulsion. The artificial pacemaker was again started with the usual immediate response.

By this time, the supply of injectable Isuprel had been exhausted and as a desperate measure, a 10 mg. sublingual tablet was dissolved in sterile water and used intramuscularly. Two mg. of Isuprel were injected. Six minutes later the artificial pacemaker was turned off. The cardiac rate at this time was 100 per minute, and the electrocardiogram showed a "slow" ventricular tachycardia. Within 50 minutes after the injection, the rate had slowed to 40 per minute. The electrocardiogram pattern was back to the usual focus for this patient.

Since the response to 0.2 mg. of Isuprel had been poor and the reaction to 2 mg. had been excessive, it was decided to try 1 mg. every hour intramuscularly and to give an extra dose if the

pulse rate should fall below the critical level of 40 beats per minute. There were no more episodes of cardiac standstill for the next 22 hours. At this time the sublingual preparation was substituted at a dose of 20 mg. every hour. He remained free of the convulsive episodes for the next five hours.

Forty-eight hours after the initial episode of asystole, acute left ventricular failure developed. Vigorous treatment with Cedilanid, digitoxin, and oxygen was instituted with a good response. Seven hours later severe failure recurred and the patient expired suddenly.

Autopsy findings: There was a recent puncture wound on the left anterior chest wall in the fourth intercostal space 2 cm. lateral to the left border of the sternum, and a second puncture wound at the inferior angle of the scapula. The intercostal muscle surrounding the puncture wound on the anterior chest wall had a "cooked" appearance for a radius of 4 mm. There were bilateral serosanguinous pleural effusions of about 200 c.c. The left lung weighed 610 grams and the right weighed 900 grams. Small, white, rounded areas with caseous centers were found in both lung fields. Marked congestion of all lobes was noted. There was a 3 by 1 cm. ecchymosis on the pericardium over the right ventricle medial to the anterior descending branch of the left coronary artery. There was a slight depression of the pericardium under this ecchymosis. There were numerous areas of fibrosis scattered throughout the myocardium. The coronary arteries showed 2+ atherosclerosis. There was passive congestion of the liver and spleen. The gastrointestinal tract showed no pathologic changes.

The positive histologic findings were as follows: (1) The alveoli of the lung were distended with a saguinous exudate, and there was congestion of the arterioles. (2) The heart showed areas of fibrosis unrelated to blood vessels. The pericardium revealed infiltration with polymorphonuclear leukocytes and red cells where the blunt-edged needle had rested against it. (3) The liver and spleen were congested. (4) There were anoxic changes in the brain.

Final diagnoses: (1) hypertensive cardiovascular and rheumatic heart disease with acute passive congestion of the lungs, liver, and spleen; (2) tuberculosis, pulmonary, inactive; (3) localized pericarditis due to cardiac stimulator electrode.

DISCUSSION

The use of Isuprel in complete heart block has been advocated by Nathanson and Miller[2-4] after testing a long series of widely used cardiac stimulants. They show that Isuprel injected subcutaneously is five times as effective as epinephrine in increasing the heart rate in patients with complete heart block. We have also found Isuprel to be more effective than larger doses of epinephrine. The dose of 1 mg. of Isuprel was larger than that recommended by Nathanson but was indicated in this patient. At a dose of 2 mg. a "slow" ventricular tachycardia was produced, but the cardiac rate and focus were returned to the usual level for this patient in about 50 minutes (Fig. 3). This would suggest that larger doses than those previously thought adequate could be used with safety in a patient refractory to the usual dose.

The constant intravenous infusion was also effective in maintaining a stimulatory action on the usual focus in this patient, even though the doses were quite small. Apparently this was sufficient to act directly on the cardiac muscle[5,6] and probably indirectly via the sympathetic nerves[6] to maintain impulse formation at an adequate rate for resting purposes. The concentration of Isuprel in the blood stream and/or the tissues remained high enough for 30 to 35 minutes after the infusion had been completed to continue this stimulant action.

Schwartz and de Sola Pool[10] have shown that exertion produces one of two effects on the rate of patients with complete heart block, a rapid increase or decrease in rate. They postulate that this change might precede an Adams-

Stokes episode. The asystole that occurred while the patient was being moved, even though the infusion was running, might be explained by this type of response to exertion. The inherent rhythmicity of the heart was restored very quickly since less than a minute was required for resumption of the idioventricular rhythm. At other times, while on the artificial pacemaker without the infusion of Isuprel, there was no resumption of the idioventricular rhythm. This was tried many times. This would indicate to us that the action of the Isuprel was important in restoration of a cardiac pacemaker.

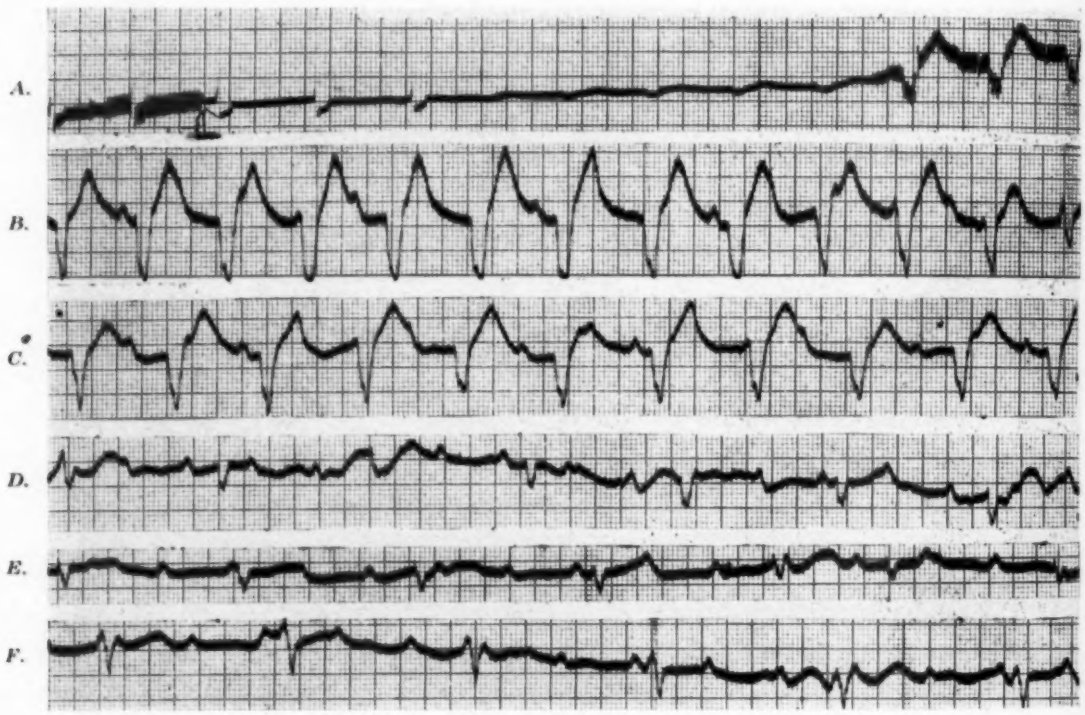

Fig. 3.—J. W. Electrical cardiac stimulator shut off (arrow in first strip) 5 minutes after 2 mg. of Isuprel had been given subcutaneously. Ventricular tachycardia in second and third strips subsided in less than 30 minutes. *A*, Five minutes after 2 mg. of Isuprel subcutaneously. *B*, Continuation of *A*. *C*, 15 minutes after Isuprel. *D*, 30 minutes after. *E*, 40 minutes after. *F*, 60 minutes after.

Whether or not the Isuprel precipitated the cardiac decompensation in this case is difficult to determine. If the stimulant action of the drug was too great for the damaged myocardium, then pushing it beyond its physiologic limit may have provoked the heart failure. Rodbard[9] has suggested that the paralysis of the bronchomotor tone plus the increased load on the left ventricle with adrenergic substances can lead to heart failure in the experimental animal. This may be an explanation in this case; however, one must remember that in the natural course of this disease, acute cardiac decompensation is very often the cause of death.

We feel that the constant intravenous infusion of Isuprel will prove to be a helpful form of therapy in cases such as this, and if continued long enough may carry the patient over a life-threatening period until a permanent pacemaker of its own is established.

SUMMARY

1. A case of complete heart block with severe Adams-Stokes syndrome has been presented.

2. A new artificial cardiac pacemaker, used for the first time, has been shown to be an effective, easily applied, safe cardiac stimulator.

3. Isuprel, given by intravenous drip or by intramuscular injection, was effective in preventing cardiac standstill in this case. The patient subsequently died of acute left heart failure.

We wish to express our deep appreciation to Drs. G. B. Myers, Muir Clapper, and Ernest Gardner for their helpful advice and criticism.

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CONGENITAL LUTEMBACHER SYNDROME

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ALTHOUGH the Lutembacher syndrome is well known and has been the subject of several articles, its congenital origin has been denied. In a recent and comprehensive review of congenital mitral stenosis[1] it is stated: ". . . we have not yet discovered a case of mitral stenosis, undeniably of congenital origin, associated with a significant defect of the interatrial septum."

In a review of the literature, we were able to find only one case of congenital Lutembacher syndrome, if by "significant defect" we accept a wide patency of the foramen ovale.[2]

In the case to be reported we had the opportunity of making a clinical, hemodynamic, and pathologic study, and it seems to us that the congenital origin of the syndrome is conclusive.

CASE REPORT

The patient, a white infant boy, was 18 months old when first examined by us. The only child of healthy parents, he was born of a normal pregnancy. He was considered a "nervous" child by his parents. He did not gain weight and seemed always short of breath.

During the last four months before we examined him, he had several episodes of fever and bronchial catarrh. At 17 months of age, an x-ray and a clinical examination revealed an abnormality of the heart.

He was a dyspneic and undernourished boy, measuring 0.78 centimeter in height and weighing 9 kilograms. No cyanosis was noted. Pulse rate, 120; respiration rate, 36. There was a slight precordial bulging. The apex beat, of a tapping character, was visible at the left anterior axillary line. At the same place a thrill was noted, but difficult to locate in the cardiac cycle. The rhythm was regular. M_1 and P_2 were markedly accentuated. There was a gallop rhythm. Two murmurs, a systolic (Grade 3) and a soft diastolic, were heard, at the second left intercostal space. At the apex a short murmur in diastole, with the characteristics of a rumble, was sometimes perceived and distinctly registered in the phonocardiogram (Fig. 1).

The neck veins were engorged. The liver was palpable two fingerbreaths below the costal margin, at the midclavicular line. The lungs were clear to percussion, but ronchi and râles were heard, specially at the bases.

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The *roentgenogram* (Fig. 2) showed an enlarged and normally placed heart, with a small vascular pedicle and slight bulging of the left middle segment. The cardiothoracic ratio was 0.60. The aorta was small and the lungs were congested and with increased vascular markings. In the right oblique view, the retrocardiac space was occupied by the heart.

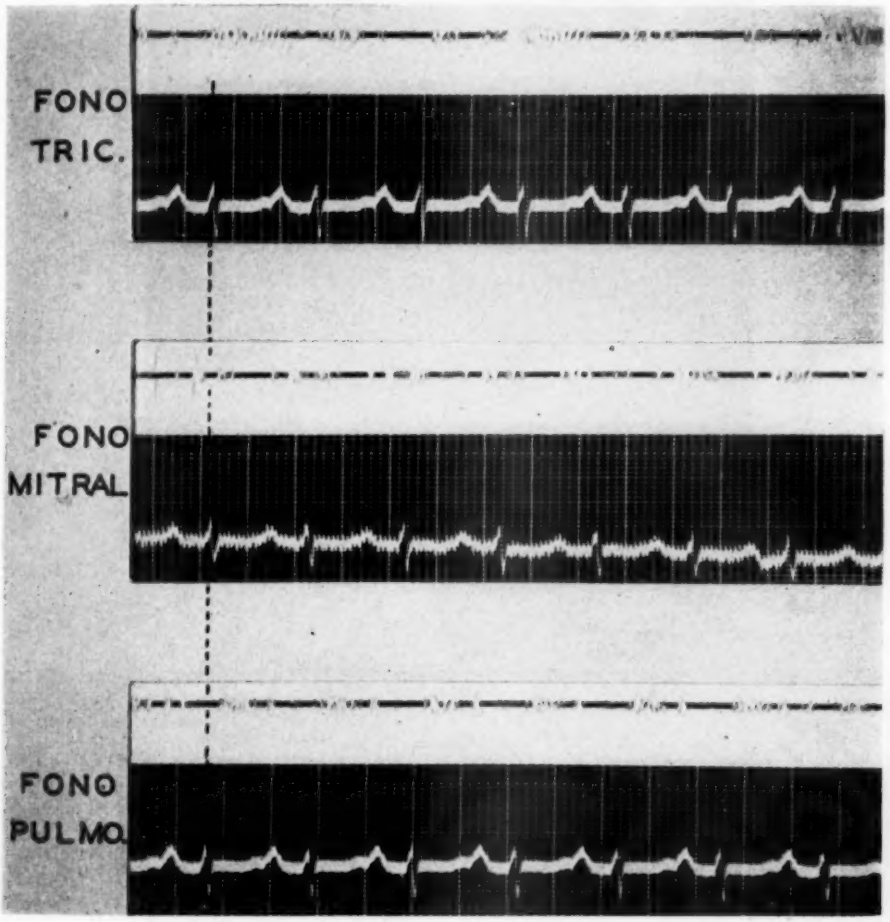

Fig. 1.—Phonocardiogram (May 3, 1953) recorded simultaneously with Lead I in the tricuspid (Fono Tric.), mitral (Fono mitral), and pulmonary area (Fono pulmo.).

The *electrocardiogram* (Fig. 3) revealed a tachycardia with sinus rhythm, rate 150. The P-R interval was 0.19 sec. P-wave duration, 0.08 sec. The P waves were deformed, tall and peaked in Leads I and II, diphasic in V_{3R} and tall and peaked in all the other precordial leads. The QRS complex had a duration of 0.08 sec. and was diphasic in Leads I, II, aV_R, aV_F and from V_E to V_6. In V_1 the $\frac{R}{R+S}$ relation was 0.54. The electrocardiographic pattern was of hypertrophy of both auricles and of the right ventricle.

Blood count: Red blood cells, 5,500,000 per cu. mm.; hemoglobin, 8 grams per cent.

The *catheterization* of the heart was made through the saphenous route and we were able to catheterize the right and left auricle and the right and left ventricle (Table I).

The data obtained from the heart catheterization proved the existence of an auricular septal defect with a marked A-V shunt.

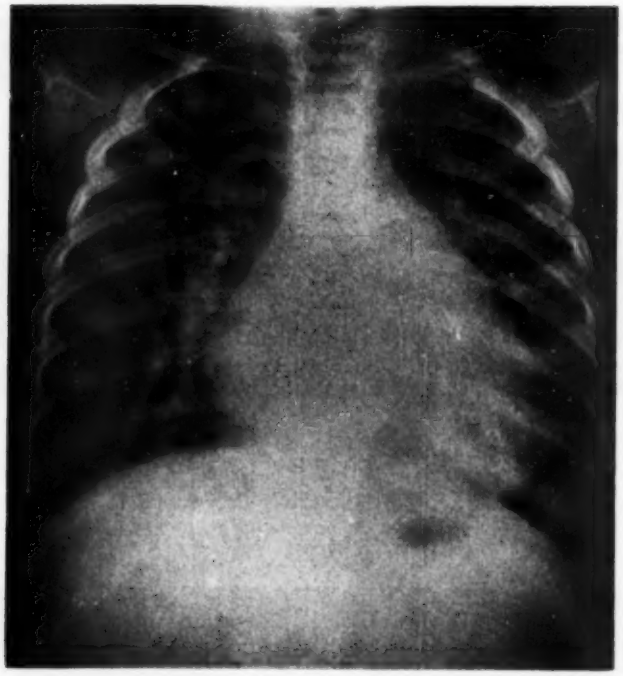

Fig. 2.—Teleroentgenogram of the heart in the posteroanterior view.

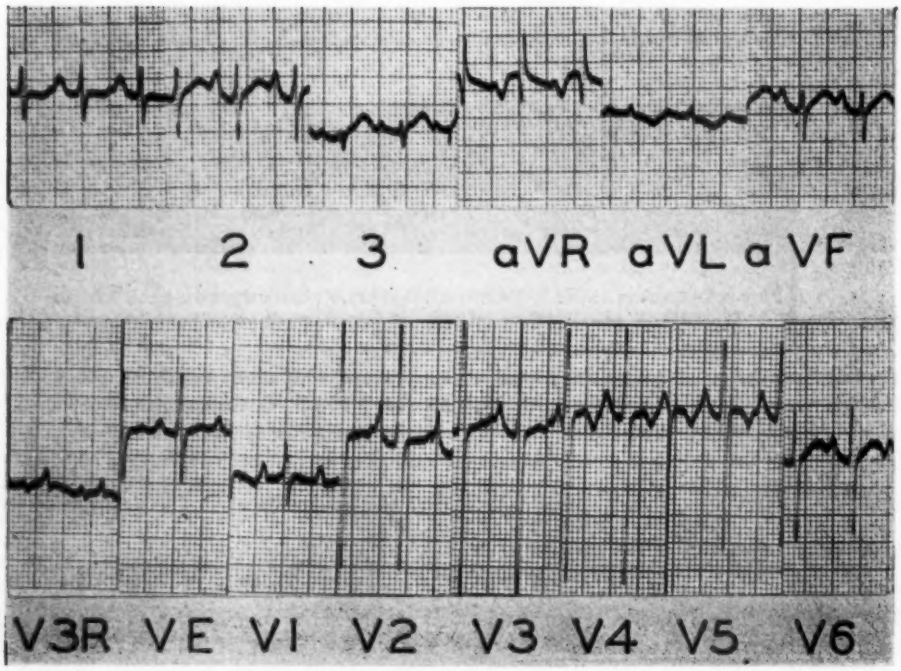

Fig. 3.—Electrocardiogram.

Fig. 4.

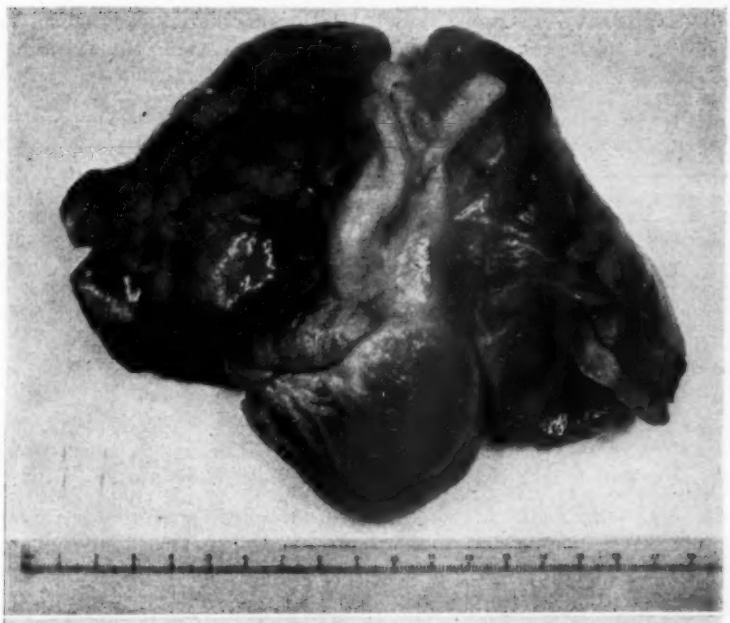

Fig. 5.

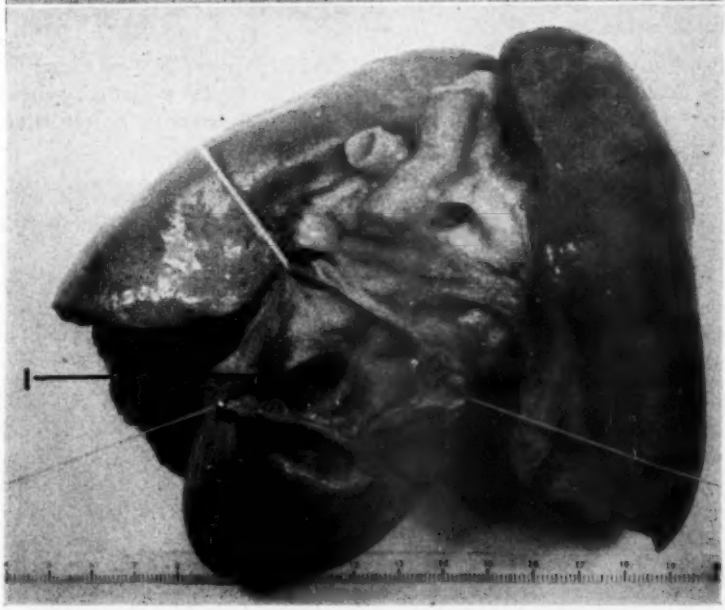

Fig. 4.—Front view of the heart and lungs.

Fig. 5.—Posterior view of the heart. The right auricle is opened and the auricular septal defect is visualized (*1*).

TABLE I

PLACE	BLOOD OXYGEN	
	VOLUME (%)	SATURATION (%)
Inf. vena cava	7.73	64
Sup. vena cava	6.22	51
Rt. auricle	10.13	84
Rt. ventricle	10.35	86
Lt. ventricle	11.80	98

An *angiocardiogram* was made in the left oblique view and the contrast-medium dilution observed in the right auricle also confirmed the interauricular communication.

The diagnosis of Lutembacher syndrome was established, based on the mitral murmur, the electrocardiographic and radiologic signs of left auricular enlargement and on the catheterization results.

The patient was submitted to a severe treatment with low-sodium diet and digitalis, without any improvement whatsoever.

We decided on surgery, hoping to relieve the mitral stenosis. Some hours before the operation was to be made, the baby, still in the ward, developed frank pulmonary edema and surgery was precipitated. The surgeon (F. A. P.) found a markedly stenotic mitral valve, but unfortunately the heart stopped during the digital commissurotomy.

Autopsy.—The heart was of normal shape, slightly enlarged, with marked bulging of the pulmonary conus (Fig. 4). The apex of the heart was formed by the right ventricle. The pulmonary artery had a normal origin, was dilated, measuring 20 mm. in diameter and the main left branch and the main right branch, respectively, 10 and 15 mm. in diameter. The aorta had a normal implantation, was smaller than the pulmonary artery and measured 16 mm. All the aortic branches were normal. The ductus arteriosus was occluded. The implantation and number of pulmonary veins and venae cavae were normal.

The right auricle was of increased size, its wall measuring 4.5 mm., and the left auricle, of normal size, had a wall thickness of 4 mm. The interauricular septum had a large defect, measuring 11 x 18 mm., localized at its inferior part, and with its lower border formed by the tricuspid valves (Figs. 5, 6, and 7). At the right side of the interauricular septum, on the posterior wall of the right auricle, there was an elevation, shaped like a prism with a posterior base (reliquat of a septum secundum?).

The tricuspid valve was 5.5 cm. in length, with an atypical configuration. While one of the leaflets was of normal shape, the other two were completely fused in one valve in its proximal two-thirds and still united in the distal third by a porous membrane of triangular shape (Fig. 6). The mitral valves were thickened, with fused borders, and their length was 4.8 cm. (Fig. 7).

The microscopic examination of the myocardium revealed small radiated areas where the muscular fibers were destroyed and substituted by a thin fibrillar network containing blood capillaries and histiocytes (Fig. 8). The borders of these areas had a reliquat of homogenized muscular fibers. The coronary branches seen in the examined slides were normal. The mitral valve (Fig. 9) was abnormally thick and with many cellular elements of the fibroblastic type, without leukocytes.

Lungs: The alveoli were normally expanded but the capillaries were covered by cubic cells which in some places had a thinly vacuolated cytoplasm and well-stained nuclei. Inside the alveoli there were large cells with a spongy cytoplasm and eccentric and sometimes multiple nuclei. In some areas the alveoli were filled with blood. The arteries had a well-developed and extremely cellular muscular sheet. Some arterioles had, in proportion with the thickness of the wall, a lumen relatively diminished.

In conclusion, there was a persistent ostium primum, incomplete development of the septum secundum, mitral stenosis, and tricuspid anomaly.

Fig. 6.

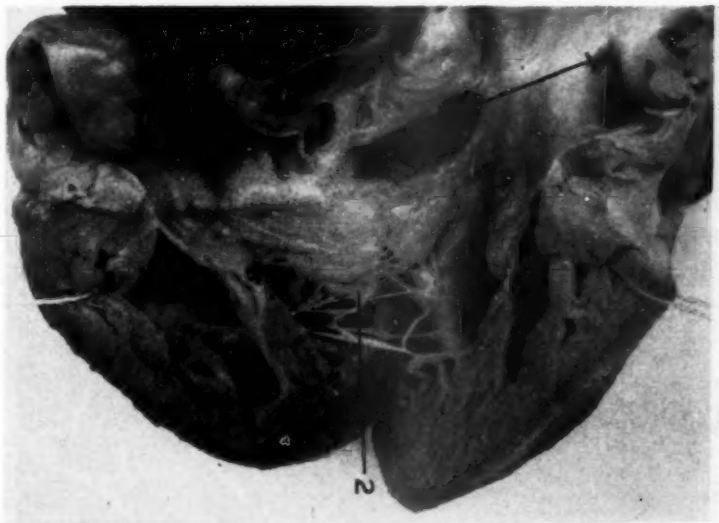

Fig. 7.

Fig. 6.—Inside view of the right side of the heart. The right auricle and ventricle are opened. *1*, Auricular septal defect; *2*, Tricuspid valve; *3*, Septum secundum.

Fig. 7.—Inside view of the left side of the heart. The left auricle and ventricle are opened. *1*, Auricular septal defect; *2*, Thickened mitral valve.

COMMENTS

The conclusion about the acquired origin of the mitral stenosis in the reported cases of Lutembacher syndrome is based mainly on the age of the patients: most of the patients reported in the world literature are adults, and several are the reports of this syndrome in old age.[3-5] With the exception of Donnaly's patient[6] who had a complex heart malformation, the youngest patient reported was 13 years old.[11]

The early age of our patient, the absence of signs of rheumatic infection, and the malformation of the tricuspid valve and of the interauricular septum, make unequivocal the congenital origin of the mitral defect.

Fig. 8.

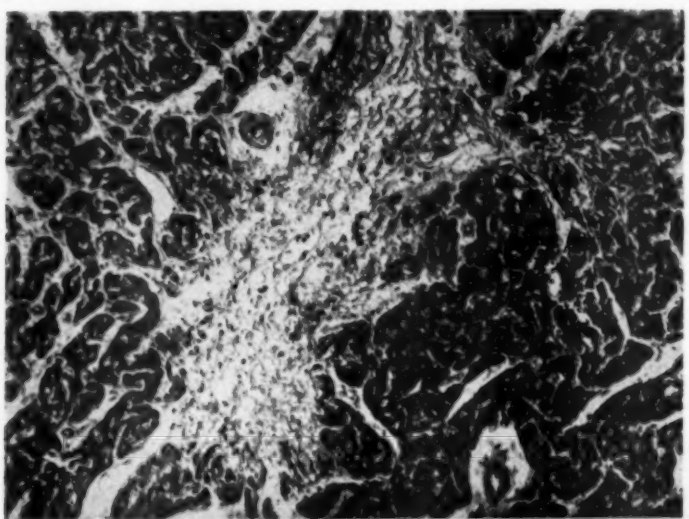

Fig. 9.

Fig. 8.—View of the myocardium; there are small radiated areas were the cardiac fibers are substituted by a fibrillar network with capillaries and histiocytes.

Fig. 9.—Thickened mitral valve with fibroblasts.

The auricular septum defect was interpreted as a "persistent ostium primum."

Since Firket,[3] all the authors[7,8] are of the opinion that, in cases of mitral stenosis, the association of an interauricular septal defect is "beneficial" for the patient, since it prevents or diminishes the pulmonary congestion. A surgical procedure[10] was even proposed, based on such an assumption.

In the present case, however, in spite of the interauricular A-V shunt, contrary to this point of view, the predominant symptoms were of pulmonary congestion and the last episode of pulmonary edema. We could speculate upon a constriction of the pulmonary veins[9] to explain the preponderance of the pulmonary congestion.

The changeable character of the mitral murmur observed in this patient is well known, and since Lutembacher,[7] it is attributed to the small blood flow by the mitral orifice.

Considering the reports on successful[1] relieving of congenital mitral stenosis, we think that these patients could be benefited with a mitral commissurotomy.

An important point to be considered in the cases of mitral stenosis of congenital origin is whether the stenosis is due to an abnormality of the mitral valve development or to a valve infection "in utero." The absence of signs of valvular or myocardial infection, plus the tricuspid anomaly are in favor of an abnormality in the valvular development.

SUMMARY

A patient, 18-months-old, is reported whose clinical, roentgenographic, electrocardiographic, and cardiac catheterization findings were indicative of a Lutembacher syndrome. Surgical relief of the mitral stenosis was attempted, but the patient expired.

Autopsy revealed a persistent ostium primum, mitral stenosis and an anomaly of the tricuspid valve which were concluded to be of congenital origin.

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PRIMARY PERICARDIAL MESOTHELIOMA

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AT the present time only twenty-five cases of pericardial mesothelioma have been reported, and all of these have recently been reviewed.[1] The following is a clinical and post-mortem report of another such case.

CASE REPORT

M. G. G., a 27-year-old white housewife was admitted to Emory University Hospital on Sept. 25, 1950, for evaluation of an enlarged heart and symptoms of congestive failure. She had been in good health until five months before admission when a routine chest x-ray (Fig. 1) revealed an enlarged heart. At this time there were absolutely no symptoms, and her physician was unable to detect any cardiac murmurs. Three months prior to admission she noted a moderate dry, hacking, nonproductive cough. About one month later she began to develop pedal edema, slight dyspnea on exertion, orthopnea, and weight gain. The edema progressed to involve the abdomen and about two weeks prior to admission she was digitalized with digitoxin and given a mercurial diuretic with good results. The hacking cough persisted and seemed to be exaggerated by a change in body position from supine to erect or from side to side. At no time was the cough productive or severe enough to make her uncomfortable. There had been no anorexia, palpitations, chills, fever, night sweats, hemoptysis, or chest pains, and the past history was noncontributory.

On physical examination she was afebrile, respirations 20 per minute, pulse 76 per minute, weak and paradoxical, and had blood pressures of 90/82, 92/82, and 98/78 mm. Hg in the left arm, right arm, and left leg, respectively. She was thin and appeared somewhat emaciated. There was evidence of bilateral pleural effusion to about the level of the angle of the scapulae. The heart sounds were very distant. The rhythm was normal sinus and no murmurs, gallop, or any friction rubs were audible. There was venous distention in the arms and neck, and the liver was palpable about two fingerbreadths below the right costal margin.

Laboratory study disclosed a red blood cell count of 6.49 million per cu. mm., a hemoglobin of 17 grams per cent, a hematocrit of 51 per cent, a sedimentation rate of 2 mm. in one hour, and and a white blood count of 10,900 per cu. mm., with 77 per cent polymorphonuclear cells, 1 per cent eosinophils, 17 per cent lymphocytes, and 5 per cent monocytes. The venous pressure in the median basilic vein of the right arm was 233 mm. of normal saline. Circulation time from right arm to the tongue was 22 seconds using Decholin.

The electrocardiogram revealed a normal sinus rate of 85 per minute, P-R interval of 0.24 second, Q-T of 0.28 second, and low voltage of the QRS (Fig. 2*A*). The changes were interpreted as being consistent with pericardial effusion and/or diffuse generalized myocardial disease, digitalis effect, and generalized epicardial ischemia. Chest x-ray (Fig. 3) revealed bilateral pleural effusion. Chest fluoroscopy following a right thoracentesis showed left pleural effusion, an enlarged left ventricle with very little visible pulsation, no apparent auricular enlargement by barium swallow, and good pulsations of the right ventricle. The aortic knob could not be visualized.

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She was placed on a 200 mg. salt diet and a right thoracentesis was performed with removal of 400 c.c. of straw-colored, slightly turbid fluid that contained 186 white blood cells per cu. mm., 2.5 gram per cent protein, and 1.010 specific gravity. The following day 630 c.c. of similar fluid was removed from the left thorax. The third hospital day a pericardicentesis was done in the left sixth intercostal space in the mid-clavicular line, and 310 c.c. of grossly bloody fluid was aspirated. This fluid had a specific gravity of 1.025, a hematocrit of 6 per cent, red blood cell

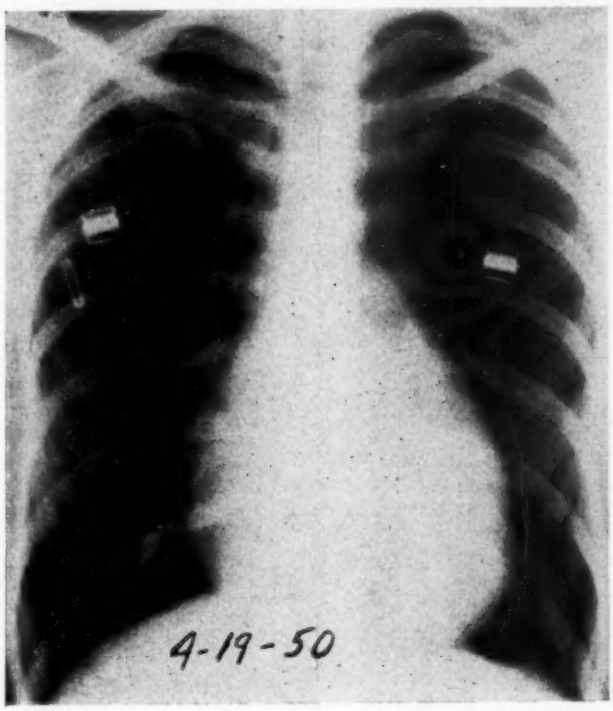


Fig. 1.—Chest x-ray showing cardiac enlargement.

count of 500,000 per cu. mm., white blood cells 200 per cu. mm. with 75 per cent lymphocytes and 25 per cent neutrophilis, and a total protein of 7.2 gram per cent. After aspiration, 150 c.c. of air and 0.5 Gm. of streptomycin were injected into the pericardial sac. Repeat fluoroscopy at this time revealed generalized cardiac enlargement, a fluid level in the pericardial sac, and a thin pericardium which contained no areas of thickening or nodules. There were no localized areas of diminished or paradoxical myocardial pulsations, but all pulsations were moderately diminished. The barium-filled esophagus was normal. A repeat electrocardiogram revealed an increase in the amplitude of all complexes (Fig. 2*B*).

There was much subjective improvement with less coughing and less dyspnea until about 12 hours after pericardicentesis when she developed anterior chest pain with a feeling of fullness in her neck. The blood pressure was 96 mm. Hg systolic and 78 mm. Hg diastolic, with a rapid, weak pulse of 120 per minute. It was thought that she had pain secondary to pericarditis and 32 mg. of codeine sulfate was given orally. Over the next two hours she became cyanotic, had no obtainable blood pressure or pulse, and a repeat pericardicentesis was done to rule out cardiac tamponade. Eight hundred cubic centimeters of bloody pericardial fluid were aspirated without any difficulty. However, she complained of severe pains in her hips, and in the sacral region of her back, and developed Cheyne-Stokes respirations during the procedure. About one hour later the pain shifted from her back anteriorly to both lower quadrants of the abdomen. She was given morphine sulfate, 10 mg. subcutaneously, as well as 50 mg. meperidine hydrochloride without complete relief. About five hours after onset of these symptoms, she became severely cyanotic, developed generalized rigidity, and died within a few minutes.

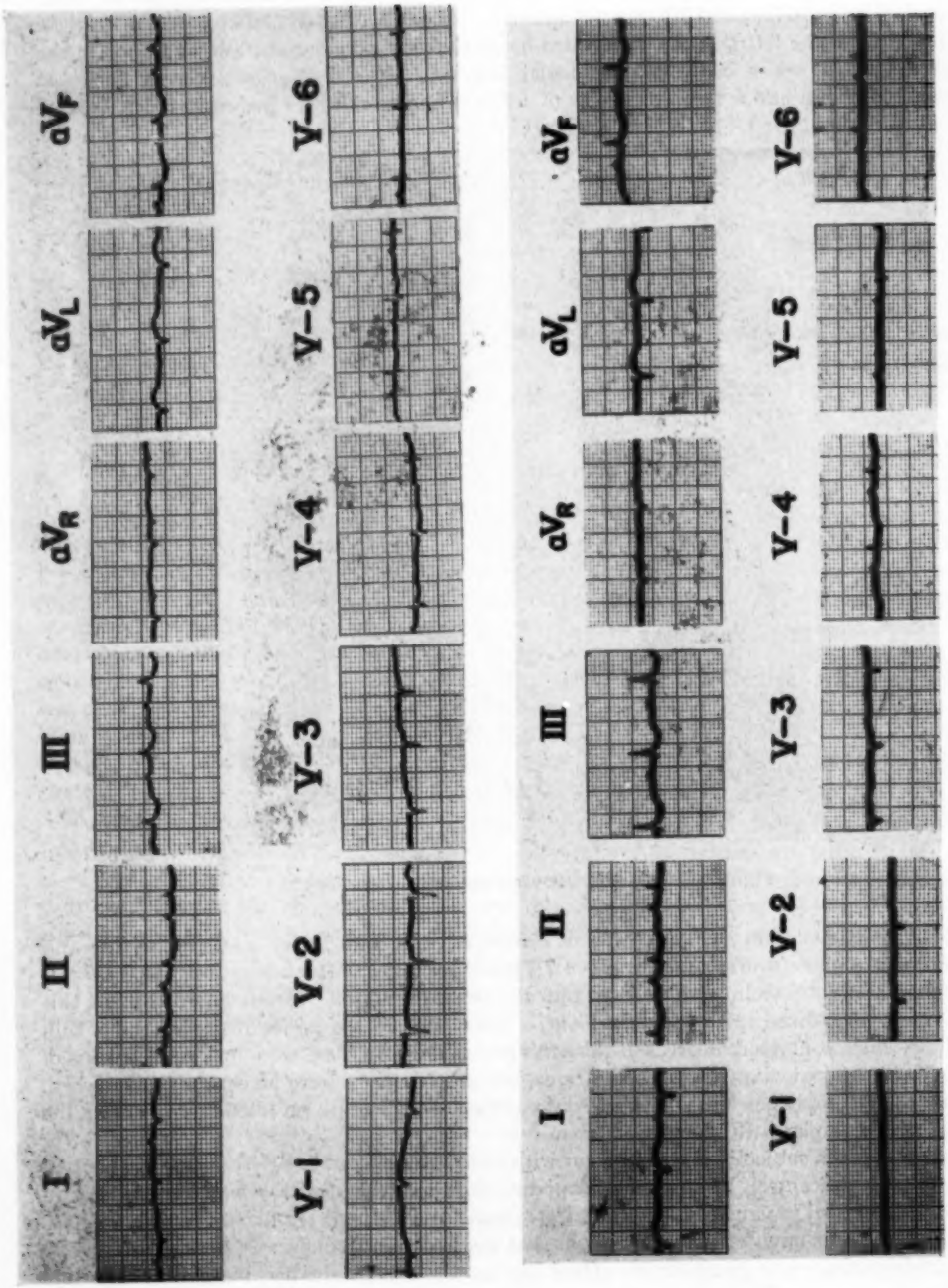


Fig. 2.—M.E.G., aged 27. *A*, The electrocardiographic study prior to pericardicentesis shows extremely low voltage, a short Q-T interval (0.28 sec.) and a wide QRS-T angle suggesting pericardial effusion, digitalis effect, and generalized epicardial ischemia. *B*, Electrocardiographic study following pericardicentesis shows increased amplitude of all complexes. The isoelectric V_1 is probably located over a large air pocket.

All fluid obtained from the pleural and pericardial spaces was thoroughly studied for acid-fast organisms, and none were found. A hemagglutination titer for tuberculosis was negative as were guinea pig inoculations. Cytologic study of the pleural fluid failed to reveal tumor cells, while smears of the pericardial fluid revealed cells that were large with only moderate amounts of dark-staining eosinophilic cytoplasm and large oval nuclei. The nuclei consisted of a dense network of granular, deep-staining nuclear chromatin.

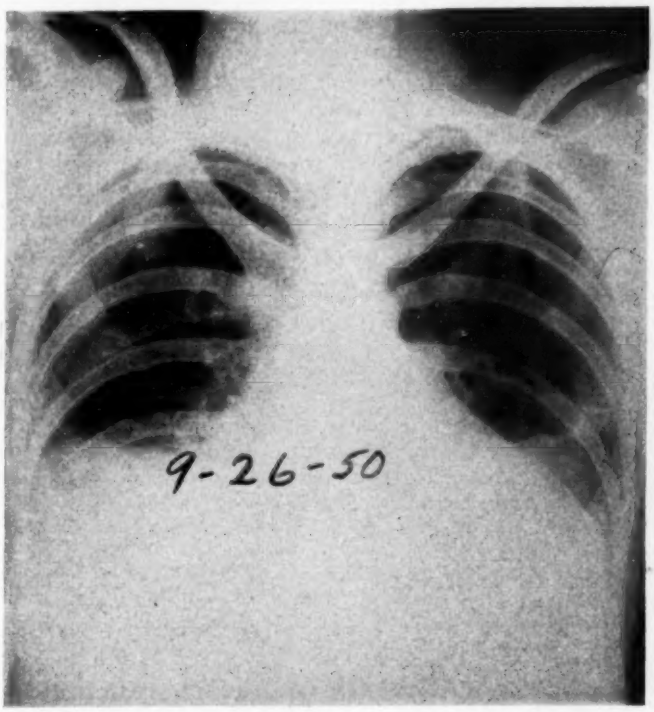


Fig. 3.—Chest x-ray showing bilateral pleural effusion obliterating cardiac borders, making heart size difficult to determine.

Necropsy findings: On gross examination four hours after death, there was evidence of moderate malnutrition. The skin and breasts were not remarkable. There were 300 c.c. of thick, yellow-gray, rapidly clotting ascitic fluid, 1000 c.c. of watery, blood-tinged left pleural effusion, and 1200 c.c. of turbid, yellowish-brown right pleural effusion. The pericardial cavity contained 150 c.c. of "foamy," dark, blood-tinged fluid and air.

Opening of the pericardium revealed innumerable raised tumor masses (Fig. 4). The tumor was more prominent on the parietal pericardium around the base of the heart and the atrioventricular groove. These masses were generally rounded, occasionally flattened, and measured from 1 mm. to 3 cm. in diameter. The nodules were quite firm and granular to palpation and appeared grayish-tan to pale-reddish-pink in color. Over the anterior mid-portion of the left ventricle there were gray, firm, fibrous adhesions between the visceral and parietal pericardium. There were many more tumor nodules over the left ventricle than over the right, and most of the largest nodules were scattered at the base of the heart. The nodules cut quite firmly and presented no necrosis or softening.

The heart weighed 260 grams and contained no air when opened under water. None of the chambers were enlarged, and there was no evidence of any valvular or congenital abnormalities. The coronary ostia were widely patent as were the coronary arteries. The left ventricular wall measured 0.8 cm. while the right measured 0.3 cm.

The left and right lungs weighed 210 grams and 220 grams, respectively. There were bilateral subapical pleural adhesions. The bronchi were normal, and there was only moderate pulmonary

ischemia. *B*, Electrocardiographic study following pericardiocentesis shows increased amplitude of all complexes. The isoelectric V_1 is probably located over a large air pocket.

congestion with scattered small areas of atelectesis throughout both lower lobes. The hilar nodes were not remarkable.

Examination of the spleen, pancreas, gastrointestinal tract, liver, gall bladder, adrenals, kidneys, pelvic organs, aorta, and bone marrow revealed no further abnormalities. Permission for examination of the brain and neck was not given.

Histologic findings: In general the tumor cells were elongated and oval in shape with considerable pale eosinophilic cytoplasm. Not uncommonly, secretory vacuoles were present. The nuclei were large, rounded, clear, and presented with prominent nucleoli and frequent mitoses. The cellular and stromal pattern varied from area to area. At times, the cells were in large nests and clusters resembling an alveolar arrangement and separated by wide bands of loose fibrous connective tissue. Other sections were arranged in parallel bundles with a whorled pattern, while at times the arrangement assumed the form of cystic spaces which not uncommonly contained small amounts of eosinophilic protein fluid. In a few areas the cells were arranged in a definite single-cell lining pattern (Fig. 5). The stroma was scanty and loose in some areas, while it was very dense in others. Scattered throughout the loosely arranged stroma were many lymphocytes and plasma cells.

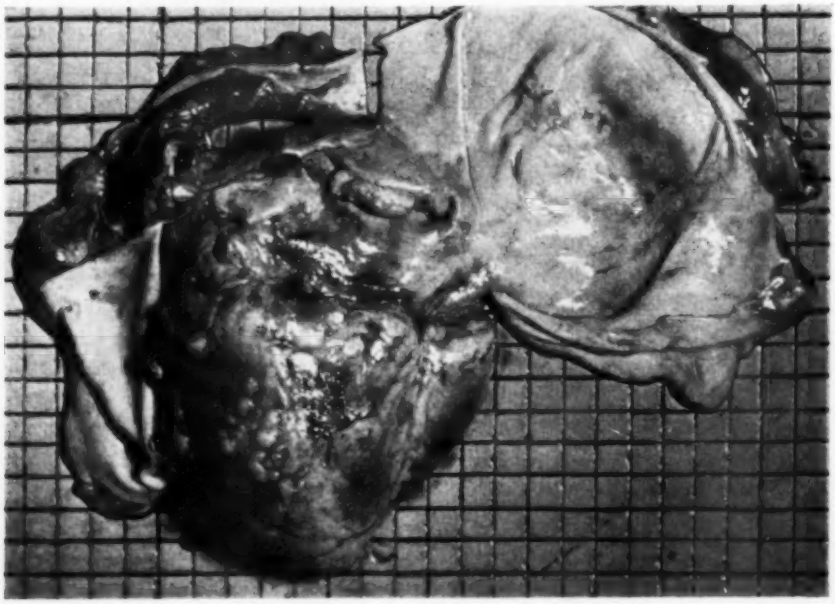


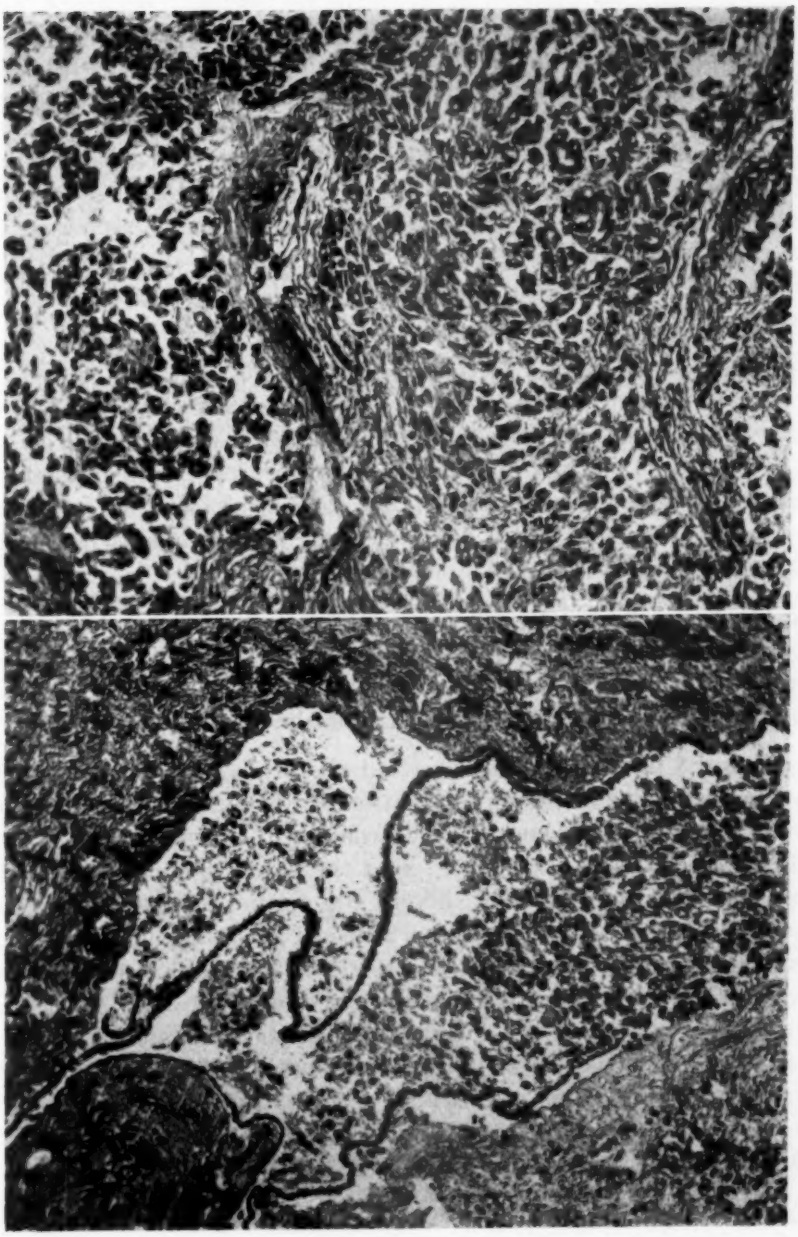
Fig. 4.—Part of the pericardium is reflected to the right. Numerous round tumor nodules may be seen over the ventricles.

There was no invasion of the myocardium even though in a few areas the myocardial fibers were slightly compressed. Frequently the neoplastic process was in close proximity to branches of the coronary arteries, but no compression or invasion was observed. Sections of the myocardium showed small patchy areas of interstitial myocarditis. The myocardial fibers were normal, but there were a few foci of interstitial polymorphonuclear leukocytic infiltration.

One hilar lymph node showed a small area of metastatic tumor in a marginal sinus histologically identified to the pericardial lesion. Sections of the remaining hilar and mediastinal lymph nodes were free of tumor. The lungs showed moderate congestion and edema and several areas of interstitial infiltration of polymorphonuclear leukocytes. The spleen also showed a diffuse polymorphonuclear leukocytic infiltration. Sections of the skin, breasts, gastrointestinal tract, pancreas, liver, adrenals, kidneys, pelvic organs, aorta, bone marrow, and spinal cord revealed no significant attention.

Final anatomic diagnosis: Mesothelioma of the pericardium with metastasis to one hilar lymph node; hemopericardium 150 c.c.; interstitial pneumonitis; acute splenitis; pleural effusions of 1000 c.c. on the left, and 1200 c.c. on the right; ascites, 300 c.c.; and congestion of the viscera.

A.



B.

Fig. 5.—*A*, Low-power view of the pericardial tumor pattern with areas resembling glandular formation. *B*, Section of the pericardial tumor showing definite single-cell lining pattern and tumor cells in the lumen.

DISCUSSION

The majority of pericardial tumors are metastatic or direct invasion from adjacent organs. In this patient, careful examination of the breasts, lungs, spleen, gastrointestinal tract, pancreas, liver, adrenals, kidneys, pelvic organs, aorta, lymph nodes, bone marrow, and spinal cord revealed no other tumor formation. The one hilar lymph node which showed a small area of tumor in a marginal sinus was histologically identical to the pericardial tumor. The histologic picture of the tumor was that of elongated, oval-shaped tumor cells with considerable pale eosinophilic cytoplasm and frequent secretory vacuoles. At times these cells were in clusters resembling an alveolar arrangement, and at other times were arranged in a definite single-cell lining pattern, all being very characteristic of a primary mesothelioma.

Prior to death, the diagnosis was not definitely established, but was thought to have been either tuberculous pericarditis or a pericardial tumor. In this case as in many others of pericardial effusion, the clinician is unable to establish quickly the etiology and not uncommonly must wait on time-consuming laboratory studies. When the pericardial effusion is bloody and associated with pleural effusion, the most likely diagnosis will be tuberculous pericarditis and specific therapy should be started as soon as possible.

The total protein content of the pericardial effusion in this case was 7.2 gram per cent. This is very high for an inflammatory process but may occur in acute exudative tuberculosis. Cytologic study as well as smears for acid-fast organisms should be carefully done but may not be diagnostic.

Meyer and Chaffee[2] in 1940 reported the study of the ascitic and pleural fluids in a patient who was diagnosed pathologically as having a mesothelioma. They found these fluids to contain hyaluronic acid in amounts of 0.174, 0.178, and 0.142 per cent. They speculated that the hyaluronic acid or "similar constituents" might, in some manner, inhibit the normal host resistance to growth of tumors. Truedsson[3] in 1951 reported a case of mesothelioma of the pleura and peritoneum in which the exudate was described as "viscous, clear, slimy, pale, amber-colored" and contained an abundance of hyaluronic acid. Blix[4] calculated the contents of the exudates described by Truedsson and found them to contain 2.7 per cent protein, and 0.7 per cent hyaluronic acid. A total of about 20 grams of hyaluronic acid was found. Dvoskin[5] reported a patient with mesothelioma of the peritoneum in which the ascitic fluid contained 4.0 gram per cent of protein and 0.103 per cent sodium hyaluronate.

Hyaluronic acid has been found in several tissues of mesenchymal origin,[2] such as the vitreous humor, synovial fluid, and umbilical cord, as well as in the mucoid phase of Group A hemolytic streptococcus. It is interesting that mesothelioma exudates seem to contain hyaluronic acid, and it is hoped that further studies will be done to determine whether this could be helpful as a diagnostic laboratory procedure.

SUMMARY

A case of a 27-year-old housewife with primary pericardial mesothelioma which had metastasis to one hilar lymph node is reported. A review of the literature indicates that mesothelioma exudates contain hyaluronic acid. Whether this is of any value in differential diagnosis cannot be determined at this time.

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ANOMALOUS INFERIOR VENA CAVA WITH AZYGOUS DRAINAGE: SO-CALLED ABSENCE OF THE INFERIOR VENA CAVA

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ANGIOCARDIOGRAPHY has become an indispensable tool in the diagnosis of complicated congenital defects of the heart. Its use has also made possible the demonstration of anomalous patterns of systemic venous return. Perhaps the most striking of such patterns is that of so-called absence of the inferior vena cava. A recent study of such a case at University Hospital has led us to review other published cases for possible similarities in the related heart defects.

CASE REPORT

G. S. was a white male infant who was noted to be questionably cyanotic at birth. Roentgenography showed the heart to be located in the right chest. No heart murmur was heard until the infant was one month of age. His color remained good, except for occasional spells of cyanosis associated with crying. Physical examination on admission to University Hospital in June, 1953, at the age of two months showed a well-appearing two-month-old infant who was cyanotic only on crying. The heart tones were very forceful and there was a Grade 1-2 systolic murmur which was about equally well heard along the right sternal margin, the pulmonic area, and over the upper left chest posteriorly. Blood pressures were normal. Roentgenographic studies showed moderate enlargement of the heart with dextrocardia; the lung markings were considered low normal or slightly decreased. The electrocardiogram showed right-axis deviation but no mirror image pattern of dextrocardia. After several days' hospitalization he was discharged with a clinical diagnosis of single ventricle with pulmonary stenosis.

He was again admitted to the hospital at the age of three months because his cyanotic episodes were becoming more severe. There had been no essential change in physical findings. Angiocardiography was carried out through the left saphenous vein. The dye was noted to pass from the iliac vein into the "azygous" vein which in turn emptied into the superior vena cava (Fig. 1); the entire heart appeared to fill almost immediately, and the pulmonary arteries and aorta showed simultaneous filling. The case seemed to have much in common with that described by Campbell and associates,[1] and for this reason it was considered probable that the same multiple cardiac defects were present: bilocular heart, pulmonary stenosis, patent ductus, and absence of the inferior vena cava. The patient was considered inoperable, and he returned home. He was again hospitalized at Children's Hospital in St. Paul, Minnesota, at the age of four and one-half months, and died four days later. Autopsy was performed by Drs. Kano Ikeda and Charles Jarvis, pathologists, who kindly furnished the following report:

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"The heart is roughly triangular in shape with the apex of the triangle pointing superiorly, the base of the triangle paralleling the domes of the diaphragm. Approximately 60 per cent of the heart is to the right of the midline. The heart weighs 65.2 grams and consists of two chambers, a common atrium and a common ventricle. There are two auricular appendages arising from the common atrium which give a false impression of normality before the heart is opened. Two hepatic veins enter the most inferior portion of the right side of the atrium independently. The pulmonary veins enter the left side of the atrium. The atrium itself is markedly dilated with rather heavy trabeculations. There is a single atrioventricular valve with two leaflets, only the posterior one of which appears fully developed. The papillary muscles are large and appear hypertrophied. The common ventricle is large. The wall of the ventricle is thickened and

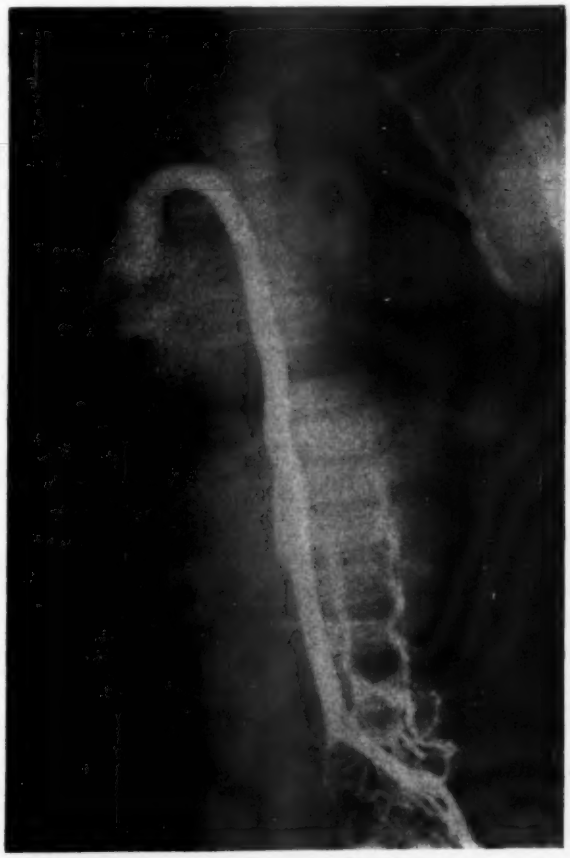

Fig. 1.—View of chest, showing filling of anomalous inferior vena cava. Note dextrocardia.

hypertrophied, firm, dark, reddish-brown in color. The trabeculations on the endocardial surface are hypertrophied. The ventricle empties into the aorta through a normal appearing aortic valve and the coronary artery orifices are normally placed. No pulmonary valve is identified, and the pulmonary artery itself is represented by a narrow cord of connective tissue approximately 2 mm. in diameter which extends from the heart to the ductus arteriosus. The right and left pulmonary arteries, which are normal in size and position, arise at a point where a remnant of the main pulmonary trunk joins the ductus arteriosus. The root of the aorta is normal and the great vessels of the neck arise normally from the aortic arch. The ductus arteriosus is large and patent. The hemiazygous vein is absent and both the right and left intercostal vessels drain into an enlarged azygous vein which empties into the superior vena cava. The common iliac

vein and the renal vein likewise empty into what is probably a persistent right postcardinal vein, in that it is continuous with the azygous vein emptying into the superior vena cava, and has no connection with the hepatic veins, both of which enter the atrium separately. *Diagnosis*: Congenital heart defect (cor biloculare with persistence of the right postcardinal vein and absence of the hemiazygous vein)."

The inferior vena cava has a complex embryologic history, being derived from portions of the postcardinal, supracardinal, and subcardinal venous systems of the developing fetus. Anomalies of the inferior vena cava are consequently very common, and the subject is dealt with in greater or lesser detail by the authors of the current texts on human embryology, such as Patten.[2] McClure and Huntington[3] published a monograph on the subject twenty-five years ago, and more recently Edwards[4] has reviewed the subject and has proposed a tentative classification of the many anatomic variations of this major systemic vein. The latter lists azygous continuation (absence of inferior vena cava) as the only common major anomaly of the suprarenal segment of the inferior vena cava. Effler and associates[5] have recently described a patient who had a pneumonectomy for pulmonary malignancy, and in the course of whose surgery a large "azygous"

TABLE I. ASSOCIATED HEART FINDINGS IN CASES OF "ABSENCE OF INFERIOR VENA CAVA"

AUTHOR	AGE	SEX	POSITION OF VISCERA	OTHER VENOUS ANOMALIES	HEART DEFECTS
Taussig,[6] 1947	25 yr.	F	Complete situs inversus	———	Dextrocardia, biloculate heart and pulmonary stenosis*
Campbell,† et al.[1] 1952	5 yr.	M	Situs inversus with levocardia	Persistent left superior vena cava	Biloculate heart, pulmonary atresia and patent ductus arteriosus*
Stackelberg, et al.[7] 1952	3 mo.	F	Apparently normal	———	None diagnosed
	1 yr.	F	Apparently normal	Persistent left superior vena cava	Evidence of atrial septal defect
Levinson, et al.[8] 1953	4 yr.	F	Apparently normal	———	Complete transposition of pulmonary veins
Downing,[9] 1953	1 yr.	M	Liver, spleen, and stomach on right	Absent right superior vena cava; persistent left superior vena cava entering left atrium	Tetralogy of Fallot and anomaly of tricuspid valve*
	5½ yr.	M	Apparently normal	Persistent left superior vena cava	Evidence of ventricular septal defect
Anderson, et al. (Present report)	4½ mo.	M	Dextrocardia	Absent hemiazygous vein	Dextrocardia, biloculate heart, pulmonary atresia, and patent ductus arteriosus*

*Died; autopsy information available.
†State in footnote that they have also seen one other case.

vein was ligated; this vein proved at autopsy to be a "persistent left inferior vena cava" (same as absence of inferior vena cava).

Except for Effler's case, the majority of recent reports of this anomaly have represented angiocardiographic findings encountered in the diagnostic workup of patients with congenital heart defects. These cases, with the associated heart findings, are summarized in Table I.

As can be seen from Table I, the cases of Taussig, Campbell and associates, one of Downing's, and the present authors', all involve either partial or complete situs inversus and have the more severe associated intracardiac defects. In three of these there was a biloculate heart. At least five of the eight cases involved anomalies of other systemic veins, usually a persistent left superior vena cava. Thus, "absence of the inferior vena cava" does not necessarily indicate any particular cardiac anomaly, although if the patient is cyanotic and there is partial or complete situs inversus one can suspect the presence of a biloculate heart with pulmonary stenosis or atresia.

Stackelberg and co-workers[7] speculated on the relative incidence of absent inferior vena cava as compared to a persistent left superior vena cava. Their two cases were encountered in a total of 100 cases of angiocardiography performed by malleolar vein injection, which would certainly suggest that the anomaly is not rare, though uncommon. Persistence of the left superior vena cava is frequently encountered in cardiac studies, and its presence in one-half of the cases reported in Table I might well be interpreted as indicating it as the more common anomaly. Our experience certainly suggests this to be true. With the increasing use of angiocardiography, especially if leg veins are used for injection, an increasing number of reports of this anomaly of the inferior vena cava can be expected. Downing[9] has suggested a diagnostic roentgen sign for the detection of this anomaly in plain films: " . . . a rounded density in the superior mediastinum which projects to the right at the position of the normal junction of the superior vena cava and right atrium. This shadow represents the dilated, anterior-coursing azygous vein as it enters the right atrium or superior vena cava."

Although the anomaly in question has been popularly termed "absence of the inferior vena cava," it has also been described as "persistence of the supracardinal system," "persistent posterior cardinal vein," "persistent left inferior vena cava," and "azygous continuation." All of these terms are somewhat misleading or vague, and one might justifiably suggest the use of a different term. It would be much more informative to say "Anomalous inferior vena cava with azygous drainage."

SUMMARY

A case of "absent inferior vena cava" is described, associated with a dextroposed biloculate heart with pulmonary atresia and patent ductus arteriosus. Seven additional cases, with heart findings, from the literature are summarized, and attention is drawn to the diagnostic implications of this anomaly. This anomaly of the inferior vena cava is best described as anomalous inferior vena cava with azygous drainage.

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Announcements

A Postgraduate Course in ELECTROCARDIOGRAPHY is to be offered by the University of Kansas School of Medicine, March 21 to 24, 1955—a four-day course providing 28 hours of basic instruction and interpretation.

The instructor will be Dr. E. Grey Dimond. For information, address: Department of Postgraduate Medicine, University of Kansas Medical Center, Kansas City 12, Kansas.

A three-day continuation course in CLINICAL HEMATOLOGY will be presented at Tulane University beginning March 23, 1955. Dr. C. V. Moore, Dean and Professor of Medicine at Washington University, has accepted an invitation to be the guest speaker. Registration is now open to all physicians but will be closed March 1, 1955.

The program will be built around actual cases insofar as possible and will include discussion of the anemias, leukemias and lymphomas, polycythemia, purpura, problems of blood transfusion, and blood coagulation. Those interested should communicate with the Director of Graduate Medicine, 1430 Tulane Avenue, New Orleans, Louisiana.

Erratum

On page 820 of the December, 1954, issue in the article "The Effect of Blood Pressure Reduction With Arfonad on Renal Hemodynamics and the Excretion of Water and Electrolytes" by John H. Moyer, W. R. Livesay, and Richard A. Seibert, the last line of Table IB should read:

		(D_1)	(D_2)	(D_3)	(D_4)		(D_1)	(D_2)
P value less than	—	.02	.01	.01	.01	—	.05	.02

and the remainder as printed.